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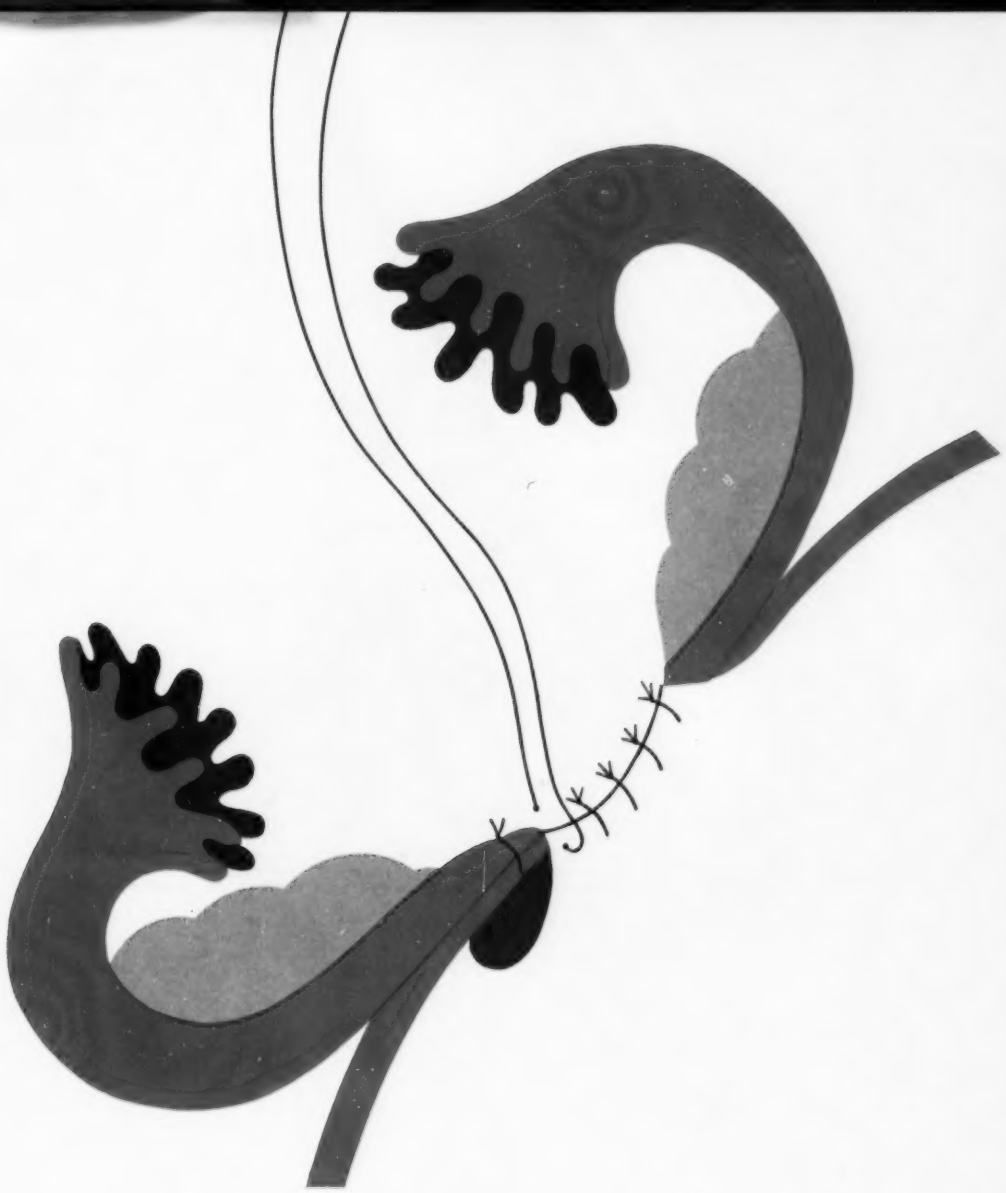

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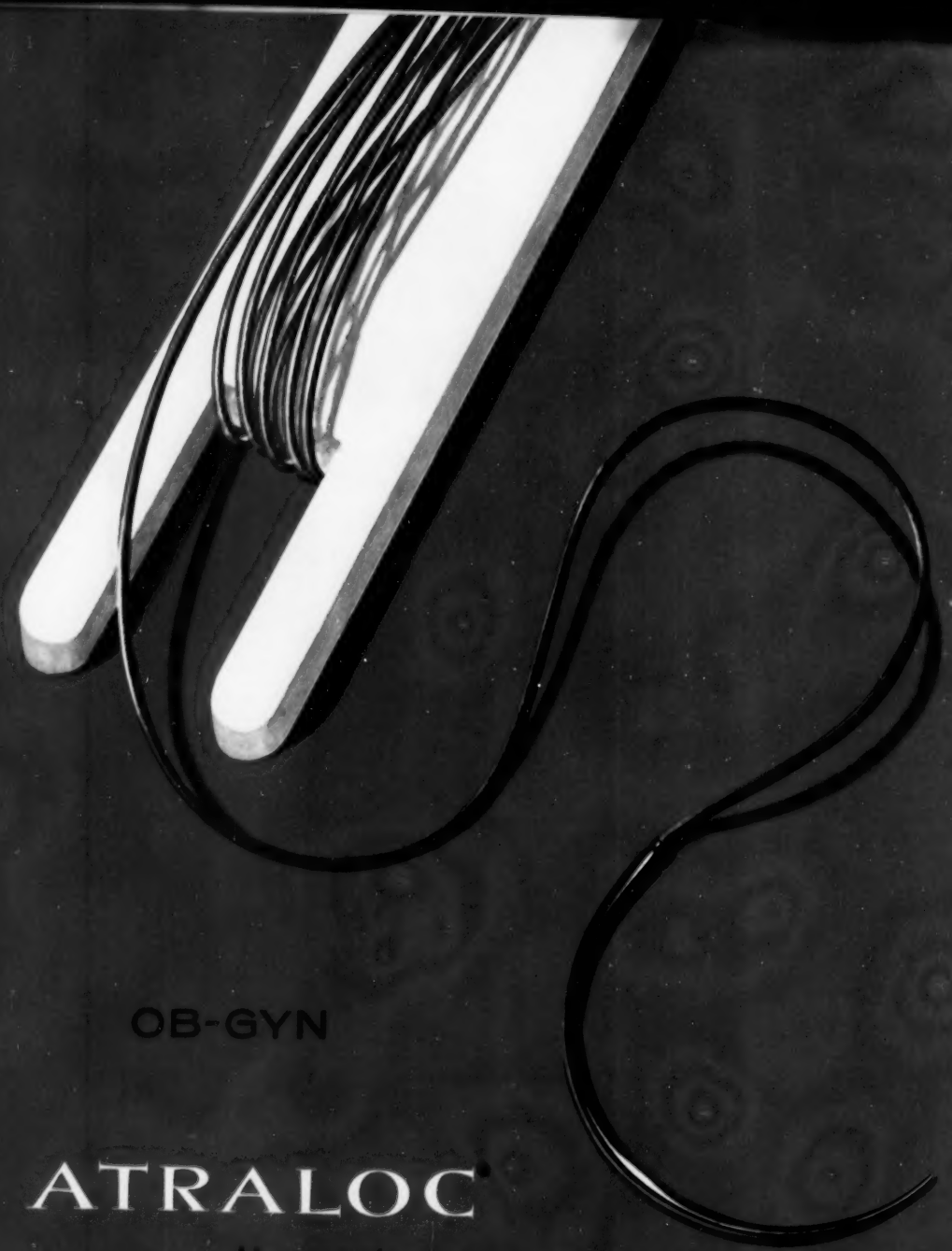

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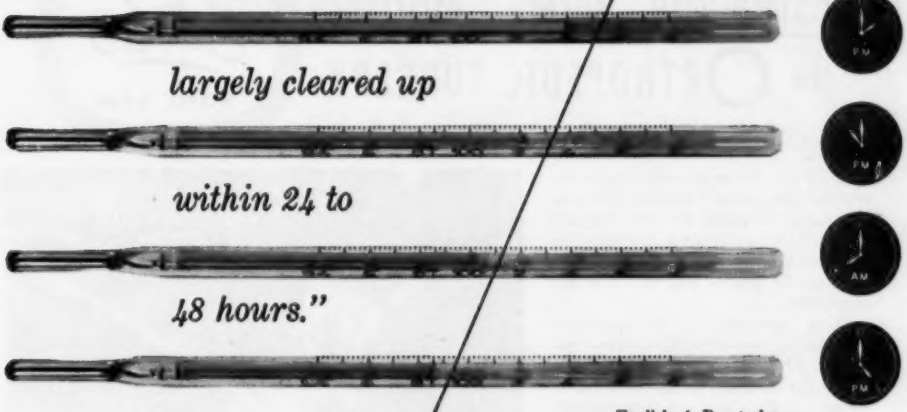

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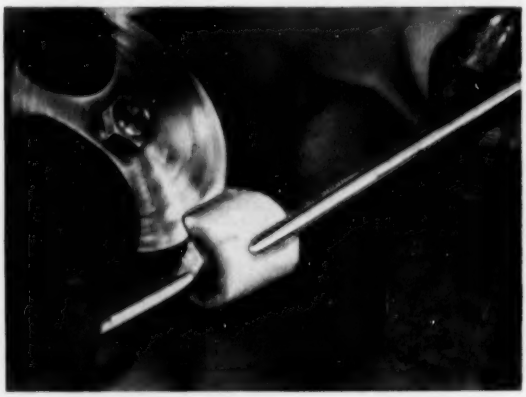

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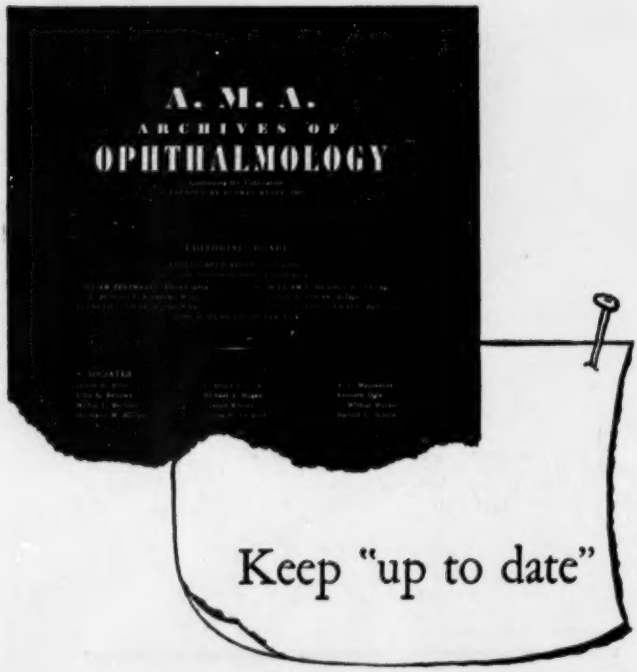

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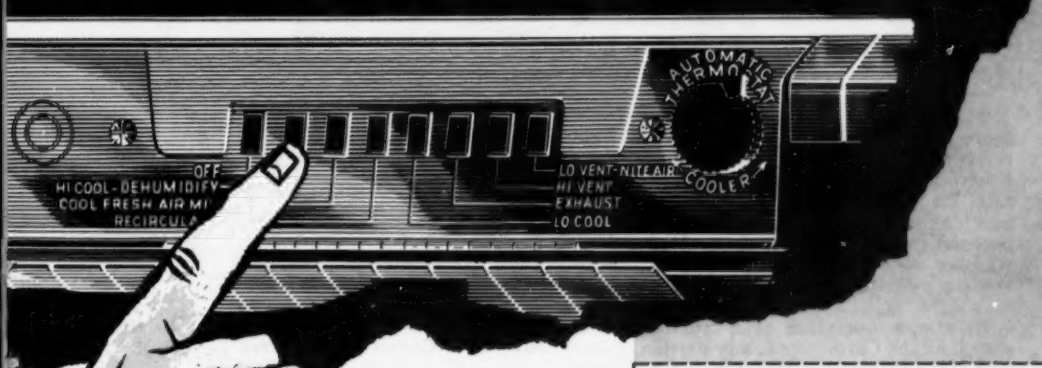

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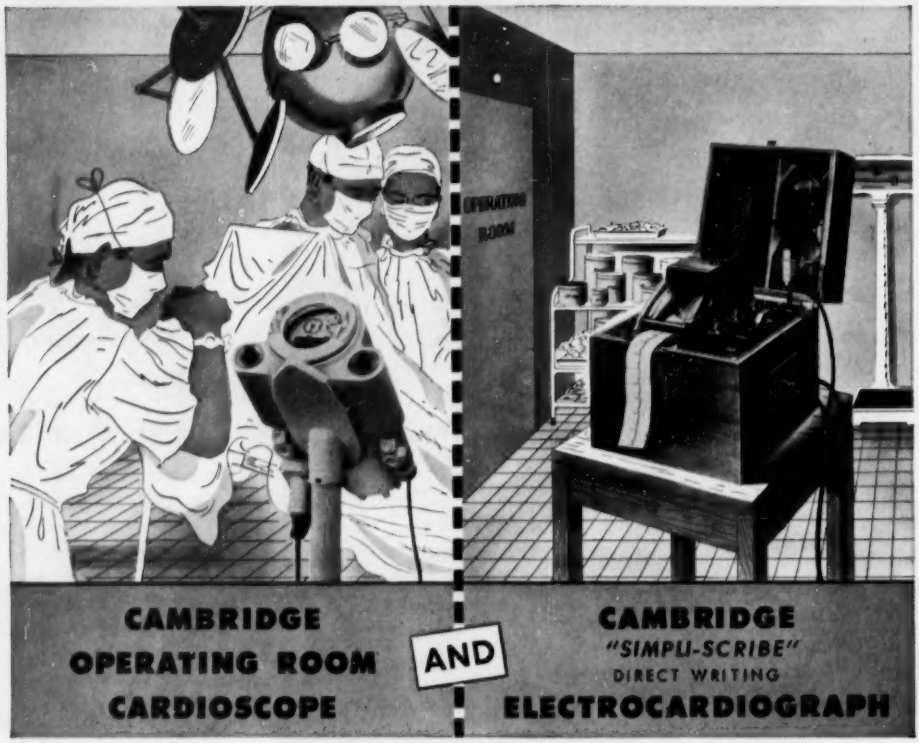

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DUCTAL CHANGES IN CHRONIC PANCREATITIS

JAMES J. BERENS, M.D.
ARCHIE H. BAGGENSTOSS, M.D.
AND
HOWARD K. GRAY, M.D.
ROCHESTER, MINN.

RECENT years have witnessed a great revival of interest in chronic pancreatitis. Clarification of its clinical findings and natural course * has led to renewed interest in surgical treatment and reevaluation of current techniques available for the management of this challenging condition.† Inasmuch as experimental studies ‡ have emphasized the importance of ductal obstruction in the pathogenesis of pancreatitis, it was thought that a thorough study of the incidence and extent of dilatation of the pancreatic ducts would be of value in determining the type of surgical procedures to be used in the treatment of this disease. We desired particularly to determine whether it was feasible to accomplish retrograde decompression of the system of pancreatic ducts by resection of a portion of the tail of the pancreas and anastomosis of the gland to the small intestine or stomach.

Although many data are available regarding the anatomy and pathology of the duct of Wirsung in the region of its duodenal orifice, a review of the literature reveals little about the condition of the remainder of the duct in cases of chronic pancreatitis. If obstruction of the duct is important in the pathogenesis of pancreatitis, it was postulated that suitable specimens would reveal dilatation of the intrapancreatic ducts; retrograde decompression would then be a logical method for treatment of the obstruction. It must be remembered that in a small but significant number of instances (4 to 10%) § the duct of Santorini is the main or sole efferent channel for the tail, body, and a portion of the head of the pancreas. Therefore special attention was given to the condition of the duct of Wirsung in the tail of the pancreas.

A number of investigators ‖ have discussed the significance of ductal obstruction in the pathogenesis of acute pancreatitis, but little attention has been given to the condition of the ducts in chronic pancreatitis. Edmondson and his associates [19] reviewed the pathologic changes in 62 cases at necropsy and stated that dilatation of the ducts is common. Popper [20] described local obstruction of small ducts in

The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Read at the Sixty-First Annual Meeting of the Western Surgical Association, Chicago, Dec. 3, 1953.

Section of Surgery (Dr. Berens, Assistant to the Staff, and Dr. Gray), and Section of Pathologic Anatomy (Dr. Baggenstoss), Mayo Clinic and Mayo Foundation.

* References 1 to 3.

† References 4 to 7.

‡ References 8 to 13.

§ References 8, 14, and 15.

‖ References 8, 16, 17, and 18.

chronic relapsing pancreatitis as a possible cause of episodes of acute pancreatitis. Cattell and Warren [7] suggested that the morbid process in both spontaneous and traumatic chronic relapsing pancreatitis derives from obstruction of the ductal system, resulting in stagnation, fibrosis, cystic accumulations, and, finally, in formation of calculi. In previous studies by Comfort, Gambill, and one of us (Baggenstoss),¶ histologic evidence of dilatation of the pancreatic ducts was noted in six cases of chronic pancreatitis, but measurements of the ducts of Wirsung in these cases were not made. Most references to ductal dilatation concern cases of pancreatic lithiasis. Johnston,[22] in 1883, noted dilatation of the pancreatic ducts as the result of occlusion by calculi. Since then, cases of pancreatic lithiasis with ductal dilatation have been reported by a number of investigators.# Whipple [27] performed radical resections of the pancreas for pancreatic fibrosis with calculi on five patients and found dilated ducts of Wirsung in four.

MATERIALS AND METHODS

The records were reviewed in all cases encountered at the Mayo Clinic from 1930 through 1951 in which postmortem diagnoses were made of chronic pancreatitis, chronic relapsing pancreatitis, and chronic recurring pancreatitis. The following criteria for acceptance in this study were fulfilled in 16 cases: (1) Diffuse changes of chronic pancreatitis were demonstrable on gross and microscopic examination; (2) pancreatitis was at least moderate to severe in intensity, and (3) the pancreas had been preserved reasonably intact for study of the ducts. Cases of pancreatic calculosis without evidence of chronic pancreatitis were not included. Cases in which neoplastic disease of the pancreas was present and those in which pancreatitis was secondary to disease in neighboring structures, such as peptic ulceration of the duodenum or stomach, were excluded. A number of cases in which gross dilatation of the pancreatic ducts was present were eliminated because the glandular changes were insufficient to meet our pathologic criteria for chronic pancreatitis.

Gross pathologic changes in the pancreas were noted, including the amount of fibrous and fatty replacement of parenchymal tissue and the presence of pancreatic fistulas. Each specimen was dissected to allow exposure of the duct of Wirsung throughout its entire length; the ducts were examined for any abnormalities, such as calculi, stenosis, or dilatation. Measurements were made of the internal circumference of the duct at three sites, namely, 4 cm. from the tip of the tail and in the midportions of the body and head. This was accomplished by opening the duct longitudinally and laying it flat so that the luminal circumference could be measured with a ruler placed transversely to the axis of the duct. Histologic sections were prepared and stained by hematoxylin and eosin. Specimens were taken from several portions of the pancreas. A control group of 11 normal pancreases was studied similarly to evaluate the size of the ducts in the cases of chronic pancreatitis.

CLINICAL FEATURES

The age of the 16 patients in this series at the time of death ranged from 28 to 78 years, averaging 55 years; only 1 patient was younger than 40. The greatest incidence of the disease occurred in the fifth and sixth decades of life. The series included 12 men and 4 women. No occupational predilection was noted. Histories were obtained of heavy ingestion of alcohol in six patients and of mild ingestion in four; abstinence from alcohol was noted in six.

All patients included in this study had experienced symptoms attributable to pancreatic disease, and 10 of the 16 had clinical diagnoses of acute or chronic pancreatitis. The duration of symptoms varied widely, with the longest clinical history extending more than 22 years and the shortest only two days. The duration of clinical

¶ References 1 and 21.

References 23 to 26.

symptoms referable to a pancreatic lesion was less than 3 months in three patients, between 3 and 12 months in eight patients, and more than 12 months in five patients. Multiple attacks of disease attributable to pancreatitis occurred in 12 patients. Eight patients had 3 or more such episodes; each of three patients had more than 10 attacks. The four patients having single clinical attacks usually had symptoms of pancreatitis that persisted until death. The diagnoses in 10 patients included some form of pancreatitis; carcinoma of the head of the pancreas with obstruction of the common bile duct was diagnosed in 1 patient.

Surgical operations were performed within two months of death in 10 of the 16 patients. Half of these operations involved the biliary tract. Seven patients died within a month of operation, and three died within the first postoperative week.

PATHOLOGIC FEATURES

Causes of Death.—The primary underlying causes of death as determined at necropsy were chronic pancreatitis in nine cases and choledocholithiasis in two. Cirrhosis of the liver, carcinoma of the lung, Cushing's syndrome, hypertension, and ventral hernia were listed as the primary causes of death in one case each. The chief contributory causes of death were general peritonitis (five cases), diseases of the liver or biliary tract (four cases), recurrent acute pancreatitis (three cases), and bronchopneumonia, edema of the lungs, uremia, and retroperitoneal abscesses (one case each).

Gross Appearance.—Extrapancreatic abscesses or encapsulated collections of necrotic material were obseved in three cases. Intrapancreatic abscesses, cavities, or pseudocysts were observed in seven cases (Figs. 1*a* and *b*). These cavities measured from 1 to 5 cm. in greatest diameter and contained variably colored necrotic material or fluid. Occasionally the fluid was clear. Usually the ducts were found to communicate with the larger spaces, but this could not always be established. The walls of these cavities were generally irregular and lined by either necrotic material and purulent exudate or a fibrous wall. Foci of necrosis that had not progressed to development of cavities or pseudocysts were observed in two cases.

A summary of the data obtained in gross examination of the pancreatic and bile ducts in these 16 cases of chronic pancreatitis is given in Table 1. Measurements of the circumferences of the ducts of Wirsung show a wide range in each region of the pancreas that was studied. These data on ductal size are analyzed in Table 2. Similar studies were made of normal pancreases to determine the abnormality of the ductal dilatation in the cases of chronic pancreatitis. Measurements of the ducts of Wirsung in 11 normal pancreases showed that the average inner circumferences at a point 4 cm. from the tip of the tail, at the midportion of the body and at the midportion of the head, respectively, were 3.0, 5.7, and 7.0 mm. The smallest measurements were 2.0, 4.5, and 4.0 mm., respectively, while the largest were 4.0, 7.0, and 10.0 mm.

For practical purposes, it can be said arbitrarily that a duct is dilated when its inner circumference is greater by at least 1 mm. than the maximal inner circumferences of normal ducts measured in a similar location. On this basis, 7 of the 16 patients in this series presented significant dilatation of the pancreatic ducts at a site 4 cm. from the tip of the tail. Three of these seven patients also had significant dilatation of the duct of Wirsung in the midportions of the body and head (Fig. 2). In only two instances (Cases 5 and 12) was the dilatation localized to the tail. Dilatation of the pancreatic ducts in the head and body did not occur without concomitant dilatation of the tail

portion of the duct, with the exceptions of Case 14, in which mild local dilatation occurred in the midportion of the head in the presence of pancreatic calculi, and Case 10, in which the pancreatic duct communicated with a cyst in the region of the head. In no instance was an organic stricture found in the duct of Wirsung. Saccular dilatation occurred in the middle of the body in two specimens (Cases 4 and 6) and in the tail in three specimens (Cases 6, 8, and 12); sometimes it was present without significant cylindric dilatation of the duct in the same region.

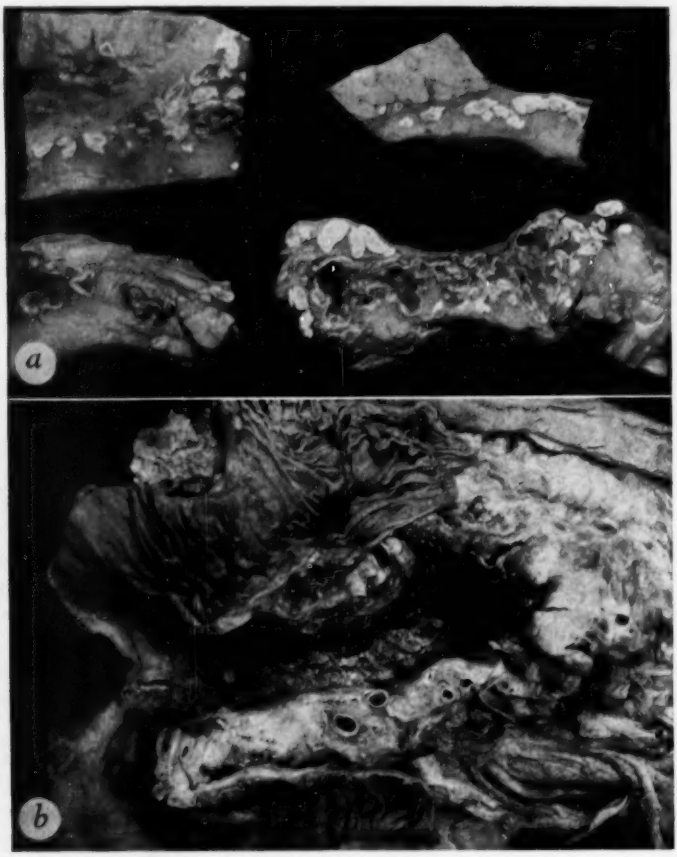

Fig. 1.—Chronic pancreatitis: (*a*), foci of parenchymal and fat necrosis with beginning cavitation; (*b*), necrosis and cavitation of head with fistula into duodenum.

Pancreatic lithiasis was present in three cases (Fig. 3). Dilatation of the duct of Wirsung was found in the head, body, and tail in two of these (Cases 2 and 9) and was localized to the head in one instance (Case 14). The duration of symptoms in patients who had pancreatic lithiasis varied from two days to nine months.

Internal pancreatic fistulas were found at necropsy in four patients (Fig. 1*b*). Pancreaticoduodenal fistulas occurred in three patients, and a pancreaticogastric fistula developed in one patient; each of these patients had undergone previous surgical procedures.

Thrombosis of the portal vein was present in six cases. Organizing thrombi were found in two of these; acute suppurative pylephlebitis with abscesses in the liver or mesentery occurred in three cases, and in one case an organized thrombus with many regions of recanalization extended from the porta hepatis throughout the intrahepatic branches of the portal vein.

Pathologic changes in the biliary tract were noted commonly. Cholecystitis had been present in 12 cases; the inflammation was subacute in 2 cases and chronic in 10. The gall bladder had been removed surgically in three cases and drained in four. Abnormal dilatation of the common bile duct was noted in seven cases, in five of

TABLE 1.—*Gross Changes in Sixteen Cases of Chronic Pancreatitis*

Case	Circumference of Lumen of Duct of Wirsung, Mm.			Pancreatic Lithiasis	Biliary Calculi		Dilatation of Common Bile Duct
	4 Cm. from Tail	Midportion of Body	Midportion of Head		Gall Bladder	Common Bile Duct	
1	2.5	3.0	3.0	—	+	—	+
2	11.0	17.0	15.0	+	—	—	—
3	3.0	7.0	10.0	—	+	—	+
4	13.0	33.0*	12.0	—	+	—	+
5	5.0	6.0	6.0	—	+	—	—
6	24.0*	30.0*	8.0	—	—	+	+
7	2.5	5.0	...	—	—	—	—
8	17.0*	8.0	9.0	—	—	—	—
9	17.0	21.0	13.0	+	—	—	—
10	3.0	5.0	30.0*	—	—	—	—
11	2.5	...	...	—	—	—	+
12	20.0*	4.0	4.0	—	—	—	—
13	2.0	4.0	4.0	—	—	—	—
14	3.0	6.0	12.0	+	—	—	—
15	3.5	5.0	8.0	—	+	+	+
16	3.0	5.0	8.0	—	+	—	+

* Saccular dilatation.

TABLE 2.—*Inner Circumference of Duct of Wirsung in Sixteen Patients Who Had Chronic Pancreatitis*

4 Cm. from Tail		Midportion of Body *		Midportion of Head †	
Circumference	Patients, No.	Circumference	Patients, No.	Circumference	Patients, No.
Less than 5 mm.	9	Less than 8 mm.	10	Less than 10 mm.	10
5 mm. or more (average normal = 3.0 mm.)	7	8 mm. or more (average normal = 5.7 mm.)	5	10 mm. or more (average normal = 7.0 mm.)	4

* Body of pancreas not suitable for study in one patient.
† Head of pancreas not suitable for study in two patients.

which cholelithiasis was present; choledocholithiasis was noted in two, whereas no biliary calculi were found in one. In four cases the common bile ducts had been explored surgically; all four ducts were dilated. Calculi were removed surgically from the common bile ducts in two cases. In only two cases (Cases 4 and 6) was dilatation present in both the duct of Wirsung and the common bile duct. Stones impacted in the ampulla of Vater were not found in this series.

Jaundice had occurred in six cases; in two of these, stones were present in the common bile duct, whereas stones were noted in the gall bladder in two others. The postmortem material used in this investigation had undergone various degrees of previous dissection, and it was not always possible to determine whether obstruction to the common bile duct was definitely produced by inflammation in the pancreas.

In at least one instance, however, the obstruction to the common bile duct was actually demonstrated to be the result of fibrosing pancreatitis (Case 1). Other causes of jaundice included calculi in the common bile duct (Cases 6 and 15), cirrhosis with hepatic insufficiency (Case 9), acute cholangitis and thrombosis of the portal vein (Case 3), and pylephlebitis with hepatic abscesses (Case 7).

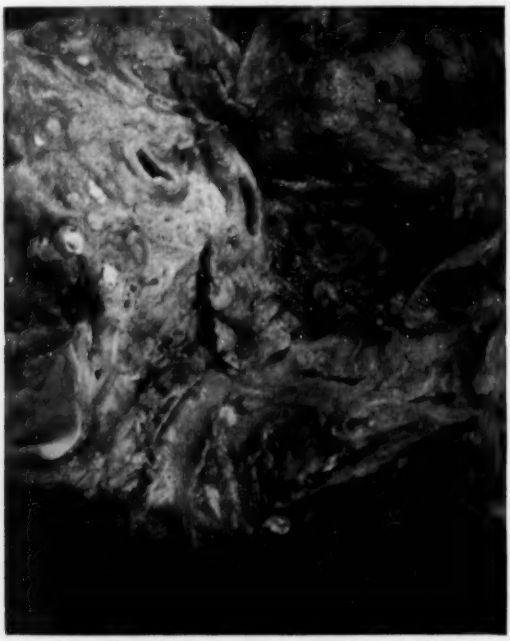

Fig. 2.—Chronic pancreatitis. Note dilatation of duct of Wirsung in the head.

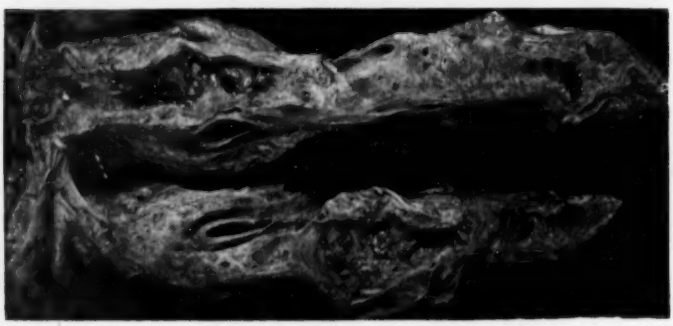

Fig. 3.—Chronic pancreatitis with pancreatic lithiasis and dilatation of the ducts.

Histologic Appearance of the Pancreas.—Fibroblastic proliferation and fibrosis were prominent features in all the pancreases examined. Lymphocytes were present in moderate numbers in seven cases and were few in nine. They were found distributed diffusely throughout the regions of fibrosis and also in focal collections. Periductal and perineural distribution of lymphocytes was prominent in a few cases.

Evidence of suppuration was found only in those cases in which necrosis or cavities were present in the pancreas. In such cases, polymorphonuclear cells and fibrin made up part of the surrounding wall. The acini were completely destroyed in the regions of necrosis and fibrosis; in other zones they were atrophic and disorganized.

Histologic evidence of moderate to severe dilatation of ductules was present in four cases; slight dilatation was noted in two cases (Fig. 4). In four of these six cases, gross examination had revealed no evidence of dilatation of the duct of Wirsung. In three other cases, however, the duct of Wirsung had been found to be dilated, yet histologic examination revealed no evidence of dilatation of the smaller ducts and ductules.

COMMENT

Either gross or histologic evidence of ductal dilatation was present in 11 of the 16 cases studied. The mechanisms producing dilatation of the pancreatic ducts can

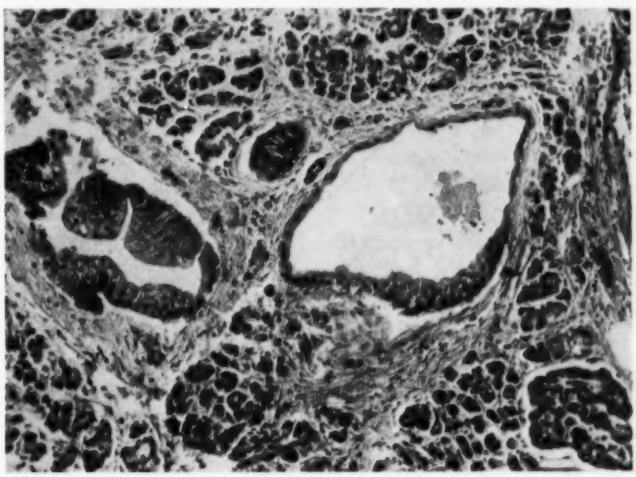

Fig. 4.—Squamous metaplasia of ducts with dilatation (hematoxylin and eosin; × 105).

be divided into two types, namely intraductal and extraductal. Intraductal causes probably were operative in three of our cases, in which calculi were observed in the duct of Wirsung. In a previous study by Haunz and one of us (Baggenstoss),[28] complete obstruction by carcinoma of the head of the pancreas produced dilatation of the duct of Wirsung in all cases studied, the mean dilatation being almost three times the normal ductal circumference. This type of obstruction, of course, is not comparable to that produced by pancreatic stones. Obstruction produced by calculi is usually partial and intermittent and probably is accompanied by inflammatory swelling of the wall of the duct.

It is difficult to evaluate the role of pancreatic lithiasis in chronic pancreatitis. Calculi are discovered occasionally in patients having no symptoms referable to the pancreas. Biopsy of pancreatic tissue,[25] as well as its histologic examination at necropsy,[26] has disclosed no evidence of inflammation in some of these cases. On the other hand, a number of observers * have noted instances of pancreatitis of many

* References 1 and 29.

years' duration before calculi are demonstrable. It is probable that in most instances pancreatic calculi are the result rather than the cause of chronic pancreatitis. In three instances (Cases 5, 8, and 12) necrotic foci involved portions of the ductal system and may have interfered with normal drainage of pancreatic juice, particularly during the regressing and healing phases of the disease.

Opie [30] has stressed the fact that an obstructing stone at the ampulla may produce a common channel (Fig. 5*a*). In one of our cases (Case 6) in which a stone was observed in a dilated common bile duct, the stone also may have obstructed the pancreatic duct (Fig. 5*b* and *c*). A biliary calculus lodged near the distal end of the common bile duct can deflect readily the thin septum separating it from the pancreatic duct to produce obstruction of the pancreatic duct. The septum at the junction of the pancreatic and common bile ducts is frequently paper-thin and could be displaced easily into the lumen of the pancreatic duct as an obstructing membrane. This mechanism has received little attention, but it appears more plausible as an etiologic factor

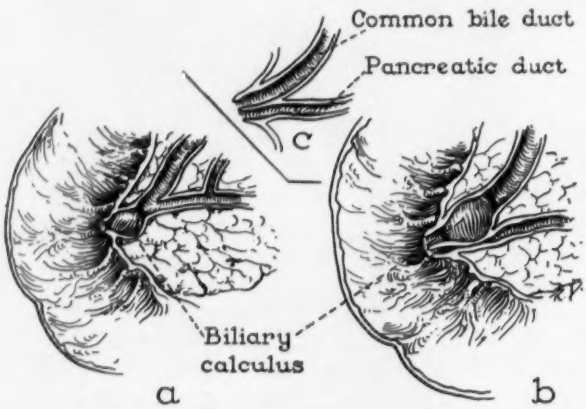

Fig. 5.—Diagram of the common bile duct and pancreatic duct entering the duodenum: (*a*), biliary calculus lodged in ampulla of Vater, producing a common channel between the biliary and main pancreatic ducts; (*b*), biliary calculus lodged in distal portion of common bile duct, producing obstruction by deflection of the thin septum across the lumen of the pancreatic duct, and (*c*), frequent anatomic arrangement of the thin septum between the pancreatic and common bile duct; this permits the obstruction shown in *b*.

in pancreatitis than the aforementioned common channel produced by an obstructing stone at the ampulla.

In one instance (Case 4), no stones were found in the dilated common bile duct, but stones were present in the gall bladder. It may be that a stone had been present in the common bile duct but had been passed before death. In this case a necrotic and cavitated zone in the head of the pancreas may have resulted in obstruction of both ducts. Obstructing metaplasia of the ductal epithelium may have been responsible for local dilatation of the small ducts and ductules observed histologically.

Extraductal mechanisms also may account for dilatation of the ducts. Spasm of the sphincter of Oddi frequently has been implicated as a cause of obstruction of the ampulla of Vater, and sphincterotomy has become an accepted surgical procedure for the relief of symptoms of chronic pancreatitis.† Actually, according to the work

† References 4 to 7 and 31.

of Mann and Giordano,[32] spasm of the sphincter because of its location causes obstruction of both the pancreatic and common bile ducts before they join. Such spasm, if repeated often enough or continued long enough, might in time result in dilatation of the duct of Wirsung. Atrophy and destruction of the parenchyma around the duct of Wirsung may produce passive widening of the duct similar to that observed in the bronchi in bronchiectasis or the ventricles of the brain in cerebral atrophy. In any event, no single cause is responsible in all cases, and it is probable that a number of mechanisms play a role, either alone or in combination.

It is interesting that of all these mechanisms, only two, namely choledocholithiasis and ductal metaplasia, can be related etiologically to pancreatitis. The other lesions that produce obstruction, such as pancreatic stones and necrotic and inflammatory foci, are generally thought to be the result of the pancreatitis. This does not, of course, imply that retrograde decompression of the pancreatic ductal system might not be effective in the treatment of chronic pancreatitis. Even though most of the obstructive lesions are not of etiologic significance, they may be important in the development of recurrent attacks and lead to progressive destruction of the gland if obstruction is not relieved. To this end, resection of the tail of the pancreas with anastomosis of the remaining portion of the pancreas to the jejunum or stomach is a method with potentialities for effective treatment. It is a much less formidable procedure than radical resection of the head of the pancreas, which eliminates the zone of obstruction of the pancreatic duct,‡ or total pancreatectomy, which has been used in some instances of advanced disease.§

Theoretic advantages of such retrograde decompression of the pancreas include reduction of the intraluminal pressure in the pancreatic ductal system caused by pancreatic secretions when the pancreatic duct is obstructed and reduction of the effects of reflux of bile into the pancreatic ducts under pressure if such occurs. A practical consideration is the selection of cases of chronic pancreatitis in which retrograde decompression may be beneficial. Patency of the duct of Wirsung in the body and tail is essential. If dilatation of the duct in the tail and body of the pancreas is necessary for successful function after pancreaticojejunostomy or pancreaticogastrostomy, this procedure would be applicable only in selected cases of chronic pancreatitis. This study revealed dilatation of the duct of Wirsung in the tail of the pancreas in only 7 of our 16 cases. It is likely, however, that dilatation of the pancreatic duct is not essential for the maintenance of such retrograde drainage, since clinical experience has shown that pancreatic fistulas are notoriously prone to stay open.

A high incidence of associated lesions or complications involving neighboring organs and vessels was present in this series. Many of these associated conditions were of such serious nature that they, rather than the condition of the ducts, might determine the course of action or require operative intervention. Among these conditions were internal pancreatic fistulas in 4 cases, portal thrombosis or pylephlebitis in 6 cases, and associated disease of the biliary tract in 12 cases. Of particular interest was the fact that jaundice occurred in six cases, in only two of which were stones present in the common bile duct. The fact that chronic pancreatitis may result in physiologic obstruction of the common bile duct has been recognized

‡ References 7 and 27.

§ References 27, 33, and 34.

for a long time and has received considerable attention in recent investigations.¶ It appears that obstruction of the common bile duct as the result of chronic pancreatitis was the cause of jaundice in at least one of our cases.

SUMMARY

Specimens of pancreas obtained at necropsy in 16 cases of chronic pancreatitis encountered at the Mayo Clinic were studied with particular reference to the presence or absence of ductal dilatation. The duct of Wirsung was found to be grossly dilated in the tail of the pancreas in seven cases. In four other cases, histologic evidence of dilatation was observed in the smaller ducts and ductules.

Factors probably contributing to the dilatation of the ducts were pancreatic lithiasis in two cases, choledocholithiasis in two cases, and foci of necrosis and inflammation in three cases. In the four cases in which histologic evidence of dilatation of small ducts and ductules was present, focal inflammatory foci or ductal metaplasia may have been responsible.

The relationship of ductal obstruction to the cause and progression of chronic pancreatitis is discussed in regard to a consideration of surgical retrograde decompression of the pancreatic duct.

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PANCREATIC CYSTS

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THE PURPOSE of this paper is to present a study of 12 cases of pancreatic cyst, an uncommon disease frequently difficult or impossible to diagnose during the early stages of its development. Accepted classifications, in general, divide these growths into two main groups: the true cyst, containing pancreatic ferments, and the false or pseudocyst, which has no epithelial lining and usually is located in the lesser peritoneal cavity. This report concerns only cysts of the retention and pseudo types.

Symptoms from which a diagnosis can be made are usually absent during the beginning weeks or even months of the disease, and not until the cyst has attained sufficient size to create pressure on the gastrointestinal, biliary, or urinary tracts do suspicious symptoms appear. Epigastric pain radiating to the back or left side was present in 85% of our cases, and a firm smooth round tumor eventually became manifest in the upper abdomen. The exact location of these masses varied with the area of pancreas involved, but, since most pancreatic cysts lie in the lesser peritoneal sac between stomach and colon or between stomach and liver, the mass usually is palpable in the epigastrium or a bit to the left. Laboratory findings are not of great value unless the disease has advanced to a degree where pancreatic destruction and necrosis has produced steatorrhea or elevation of the blood amylase. Hematuria, pyuria, and albuminuria are not common but do occur.

Roentgenographic examination is of considerable value when the cysts have attained demonstrable size. An extremely helpful outline of diagnostic x-ray findings has been compiled by Poppel and Marshak,[1] and to this further additions have recently been made by Haukohl and Melamed.[2] In brief, findings to be expected are as follows: If the cyst is located in the head of the pancreas, the duodenal curve is widened, the duodenum narrowed, and stomach and colon displaced downward. Characteristic of cysts of the tail are a compression of the posterior gastric wall and greater curvature, a deflection of the stomach to the right, and a downward displacement of the duodenojejunal flexure. An upward displacement of the stomach and a downward displacement of the colon are typical of body cysts, caused as the expansion of the cysts takes place between the two.

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Differential diagnosis of pancreatic cysts may prove quite difficult, and only by detailed study can the following be ruled out: gall bladder disease and enlargement; splenomegalies; enterogenous, omental, and mesenteric cysts; enlargements of the liver and kidneys, and, infrequently, aortic aneurysms. As emphasized by Case,[3] Brunschwig,[4] Kretchmer,[5] Abeshouse,[6] and others, renal cysts, kidney tumors, and hydronephrosis are particularly confusing.

REPORT OF CASES

CASE 1.—M. H., a 29-year-old housewife, entered the hospital Feb. 1, 1938, complaining of dull pain in the left hypochondrium present for six months with an associated marked fatigue. Recurrent attacks of sharp severe pains were superimposed on the dull pain, and these radiated to the back. She had noticed a mass in the upper abdomen, first the size of an orange, gradually getting larger. Physical examination was essentially normal except for a palpable nontender smooth round mass in the left hypochondrium. Laboratory examination of the blood and urine showed no abnormal findings. X-rays of the gastrointestinal and genitourinary tracts were negative.

A left paramedian incision was made, and an oval cystic mass approximately 20 cm. in its greatest diameter was found occupying the lesser peritoneal cavity. A large amount of brown turbid fluid was aspirated, and the cyst was marsupialized. Recovery was uneventful; the drainage spontaneously ceased, and within a year the patient went through a normal pregnancy.

CASE 2.—Dr. H. B., a 46-year-old physician, entered the hospital on July 26, 1935, complaining of mild gall-bladder attacks over a period of several years, an episode diagnosed as acute pancreatitis three months prior to admission, and dull steady epigastric pain of two months' duration. There had been no nausea, vomiting, jaundice, or abnormal stools.

Physical examination was essentially normal except for a firm smooth slightly tender epigastric mass, which did not move with respiration. Cholecystograms were normal, but roentgenograms of the stomach revealed an upward displacement and a widening of the duodenal loop. An elevated leucocyte count, 20,000, was the only significant laboratory finding.

A laparotomy was done, and a cystic pancreatic tumor pressing through the gastrocolic omentum was drained of 3,000 cc. of cloudy fluid. The thickened edges of the cyst wall were marsupialized to the anterior parietal peritoneum, and within three months the cavity ceased draining and the sinus closed spontaneously.

CASE 3.—E. S., a 39-year-old housewife, entered the hospital on Sept. 22, 1942, complaining of right upper abdominal pain and development of a right subcostal mass over a two-year period. The pain radiated to the right scapula, and the patient had lost 10 lb. (4.5 kg.).

Physical examination revealed an enlarged liver, extending two fingerbreadths below the right costal margin, and a firm smooth round mass in the epigastrium slightly to the right of the midline. Laboratory findings on the blood and urine were normal. Cholecystograms were normal. An x-ray film of the abdomen showed several small areas of calcification in the region of the pancreas, suggesting stones.

A right paramedian incision was made, and a cyst of the pancreas was drained of 150 cc. of watery fluid. The walls of the cyst were then sutured to the peritoneum, and external drainage was established. Two years later the patient returned because of a persistent drainage from her abdominal scar. The longest time drainage had stopped was two weeks, and a series of x-ray treatments had been ineffectual. The abdomen was again opened, and a fistulous tract leading to the duodenum was excised and the bowel closed. After a stormy convalescence the patient was discharged, and she was reported to be in good health five years later.

CASE 4.—J. N., a 35-year-old housewife, entered the hospital on Aug. 21, 1934, complaining of upper abdominal pain, unrelated to food intake, recurrent for three years. A fullness had developed in the epigastrium during the past year, and backache was present most of the time.

Physical examination was essentially normal except for the presence of a firm smooth mass in the epigastrium, which did not move with respirations. Laboratory findings on the blood and

urine were normal. Cholecystograms showed a nonfunctioning gall bladder. Roentgenograms of the stomach revealed a widening of the duodenal curve and a downward displacement of the stomach.

A right paramedian incision was made, and the abdomen was entered by freeing multiple adhesions. A large cystic mass bulged through the gastrocolic omentum, from which clear fluid was aspirated. External drainage was established by suturing the walls of the cyst to the peritoneum and fascia. The patient refused to return to the hospital three months later, when drainage suddenly ceased, and died of peritonitis due to rupture of the cyst into the abdominal cavity.

Case 5.—L. C., a 52-year-old housewife, entered the hospital on March 20, 1947, complaining of recurrent epigastric pain, fatigue, and backache for 14 months. She was afraid to eat and had lost 30 lb. (13.6 kg.).

Physical examination revealed a firm smooth mass in the upper abdomen, which appeared to move with respiration. Laboratory findings on the blood and urine were normal. Cholecysto-

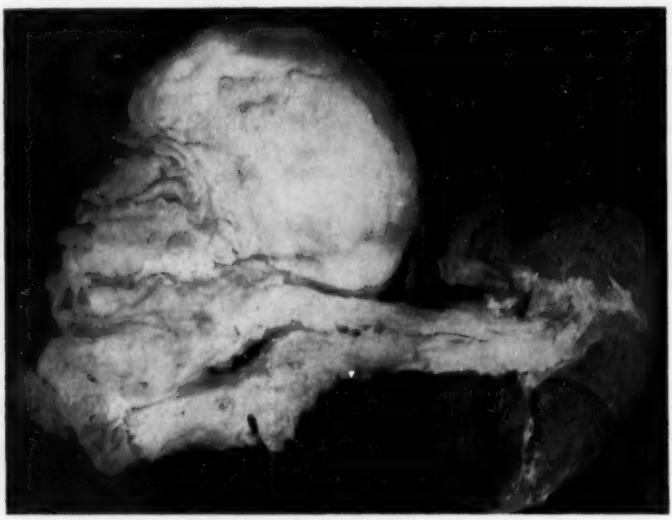

Fig. 1 (Case 7).—Photograph of excised cyst, pancreatic tail, and spleen.

grams showed a nonfunctioning gall bladder. An extrinsic mass posterior to and deviating the stomach to the left was seen in roentgenograms.

A right paramedian incision was made, and a cyst of the pancreas was drained externally of 200 cc. of watery brown fluid. Postoperative recovery was uneventful.

Case 6.—M. G. S., a 33-year-old housewife, entered the hospital on April 14, 1944, complaining of a "lump" in the left upper abdomen, which had gradually increased in size for the past nine months. Shortly preceding discovery of the mass she had noticed a dull pain below the left costal margin, which increased in severity and traveled through to the back. On physical examination a large nontender mass extending from the epigastrium into the left upper quadrant was palpated. Laboratory findings made of the blood and urine were normal. Roentgenograms of the genitourinary tract showed no evidence of pathology. At fluoroscopy the colon was seen to be deflected downward at the splenic flexure by a soft-tissue mass, and the stomach likewise was displaced by this same mass.

When the abdominal cavity was opened, the stomach and transverse colon were seen to be pushed forward by what proved to be a large pancreatic cyst. Aspiration of 1,000 cc. of fluid

was done, and, because of the blood supply, it was necessary to remove the spleen along with the cyst. Convalescence was uneventful, and three years later the patient delivered a full-term normal female child.

CASE 7.—S. E., a 31-year-old farm wife, entered the hospital on Oct. 29, 1944, with complaints of upper abdominal pain recurrent for three years and a mass in the right upper quadrant which had developed one year previously. This had been drained by her family doctor and continued to drain.

Physical examination was essentially normal, except that she was underweight, 97 lb. (44 kg.), and had a draining fistulous tract in her abdominal scar. Laboratory tests were noncontributory. Opaque material injected into the fistulous tract partially outlined a cavity to the left and anterior to the 12th thoracic vertebra.

Laparotomy revealed a cystic tumor arising from the body and tail of the pancreas, approximately the size of a pineapple. The tumor along with the body and tail of the pancreas and spleen were removed en masse (Fig. 1). Recovery was uneventful.

CASE 8.—J. R. D., a man, aged 47, entered the hospital on April 28, 1952, complaining of upper abdominal pain and back pain for a period of two years. Ten years previously he had experienced an attack of severe epigastric pain with high temperature and was operated upon for an infection in the pancreas. Five years ago (1947) he had recurrence of the pain and was not relieved by aspiration of a pancreatic cyst. A splanchnicectomy was then done to relieve the pain.

Physical examination was essentially normal except for healed operation scars and slight tenderness on palpation below both costal margins. Blood and urine tests were normal. Areas of calcification were seen to the right of the third and fourth lumbar vertebrae by fluoroscopic examination. Cholecystograms revealed a nonfunctioning gall bladder.

A laparotomy was done, and, after multiple massive adhesions were freed, a cyst of the pancreas approximately 9 cm. in diameter was evacuated by aspiration. The duodenum and ampulla of Vater were opened in search of a calculus, but none was found. Internal drainage of the cyst by means of a two-row anastomosis between cyst and duodenum was done. An opportunity was afforded to inspect the anastomosis at a later date, when the patient died of a lung condition. The cyst was found collapsed, and the anastomosis was intact and patent.

CASE 9.—S. R., a 36-year-old laborer, entered the hospital on June 15, 1950, complaining of epigastric pain, nausea, and vomiting for four days. A similar episode had occurred two years previously after excessive drinking and overindulgence in rich food. A diagnosis of duodenal ulcer had been made at that time, substantiated by x-ray films in his possession.

A slightly tender firm smooth rounded tumor was palpable in the epigastrium, and bowel sounds were hypoactive; otherwise, physical examination was essentially normal. Laboratory tests showed normal urine and red cell counts. The white cell count was elevated to 10,000, and a later gastric analysis revealed free acid of 40 and total acid of 60 units. Roentgenograms failed to disclose the previously diagnosed duodenal ulcer, but evidence existed of an extrinsic mass exerting pressure on the stomach and increase of the duodenal sweep.

The abdomen was entered through a left paramedian incision, and the duodenum and gall bladder were found to be normal. When the lesser peritoneal sac was opened, a cyst was seen which occupied the center of an inflammatory mass involving the pancreas and surrounding tissues. From this, 600 cc. of fluid was aspirated. Excision was considered but abandoned for what appeared to be the more favorable procedure of cystojejunostomy. Recovery was uneventful, and two years later the patient reported having no symptoms.

CASE 10.—M. W., a 53-year-old housewife, entered the hospital on Jan. 2, 1950, complaining of recurrent attacks of epigastric pain, which at times shifted to the right or left or again to the back. Occasionally these attacks were accompanied by slight chills and a low-grade fever. During a period of three years she had been in three hospitals. Physical examination was essentially normal except for a large smooth firm slightly tender mass in the left upper quadrant. Blood and urine examinations were normal. Roentgenograms and fluoroscopy showed an extrinsic mass causing a deformity of the greater curvature of the stomach and a narrowing and downward displacement of the splenic flexure of the transverse colon. A left upper paramedian incision

was made, revealing a cystic mass arising from the pancreas. Aspiration of 600 cc. of fluid was done, and a two-row cystojejunostomy was completed. Postoperative recovery was uneventful, and the patient has remained asymptomatic.

Case 11.—H. K., a 57-year-old male musician, entered the hospital on Feb. 17, 1948, with a history of recurrent attacks of epigastric pain for a period of three years. These attacks usually lasted from one to two hours; the pain radiated to the back and was not related to the type of food eaten. Seven months prior to his admission he had been operated upon in another city, where a pancreatic cyst was marsupialized. After this procedure drainage of small amounts of clear fluid from his abdominal scar had continued, and it was necessary for him to take small doses of insulin to control a slight amount of sugar which was present in the urine.

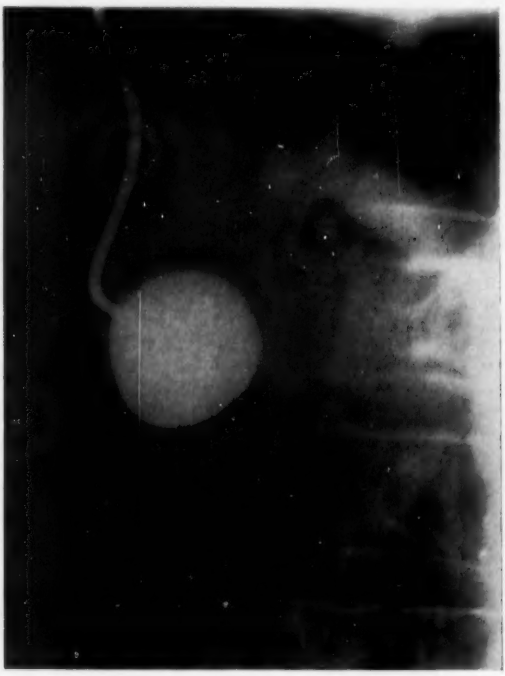

Fig. 2 (Case 11).—Roentgenogram showing appearance of radiopaque material in fistulous tract and cyst.

Physical findings were noncontributory except for a draining fistula in the abdominal scar, about which there was some redness of the skin. Laboratory findings were essentially normal. Amylase readings varied from 68 to 120 mg. per 100 cc. Roentgenograms of the stomach and colon were normal. Upon injection of opaque material into the fistulous tract, a large cystic cavity was demonstrable (Fig. 2).

Multiple firm adhesions involving the spleen, stomach, diaphragm, gastrocolic omentum, pancreas, and fistulous tract were encountered at operation. En bloc excision to include cyst, fistulous tract, tail of pancreas, and spleen was done. Postoperative recovery was uneventful, and the patient no longer needed to take insulin.

Case 12.—P. G., a 33-year-old man, entered the hospital on Oct. 15, 1952, complaining of back pain for a period of three years, with recurrent attacks of epigastric pain, nausea, and vomiting for one year. Diagnoses of lumbosacral sprain, peptic ulcer, and gall bladder disease had been previously made. Medical management of these conditions had failed.

Physical examination revealed no essential abnormalities except in the abdomen, where moderate tenderness and an ill-defined small mass was found in the epigastrium. Electrocardiographic, Kahn, urine, hemoglobin, and red cell examinations were all normal. The leucocyte count was 16,500, with a preponderance of polymorphonuclears. Serum amylase was 87 mg. per 100 cc. Previously taken x-ray films showed a nonvisualizing gall bladder and evidence of an extrinsic mass exerting pressure on the stomach.

Within a few days after the patient's admission, the mass in the abdomen began to increase in size and rapidly reached 8 cm. in its greatest diameter. A laparotomy revealed an inflammatory process involving the pancreas and surrounding structures. Included was a pancreatic cyst, containing 200 cc. of amber fluid, firmly embedded in the lesser peritoneal cavity. An excision of the cyst was considered unwise, and cystojejunostomy was done, with use of the Roux-Y method, placing a loop posteriorly through the mesocolon. Postoperative recovery was uneventful, and the patient has continued to remain symptom-free for over a year.

TABLE 1.—*Results in Previously Reported Cases of Pancreatic Cyst Treated by Internal Drainage*

Operation	Cases, No.	Results	
		Poor	Good
Cystogastrostomy	52	7	45
Cystoduodenostomy	12	2	10
Cystocholecystostomy	11	3	8
Cystojejunostomy	43	6	37
	118	18	100

TABLE 2.—*Results Obtained in This Series of Cases Following Various Methods of Treatment*

Case	Age, Yr.	Operation	Results
1	29	Marsupialization	Good
2	46	Marsupialization	Good
3	39	Marsupialization	Poor
4	35	Marsupialization	Poor
5	52	Marsupialization	Good
6	33	Excision of cyst	Good
7	31	Excision of cyst	Good
8	47	Cystoduodenostomy	Good
9	36	Cystojejunostomy	Good
10	53	Cystojejunostomy	Good
11	57	Fistulectomy	Good
12	33	Roux-Y	Good

Since so few cases have been treated by any one surgeon or in a single institution, the relative merits of various surgical procedures are obviously not easy to evaluate. In the above cases all available methods of treatment, namely, excision, external drainage, internal drainage, resection, and sphincterotomy, were used. When feasible, total excision is the accepted operation of choice. However, the frequent technical difficulties encountered and a mortality rate of over 50% from unsuccessful excision attempts have limited its use to a small percentage of cases. In our series this procedure was used in three cases; in one a primary resection was done, and in the other two the cyst was resected along with a fistulous tract as a secondary operation following marsupialization.

External drainage or marsupialization is the simplest of all procedures; has been most widely used; has a low mortality rate, of 4 to 6%, and is particularly valuable for drainage of a pseudocyst whose walls cannot be resected or anastomosed. Objec-

tions to this type of operation are the possibility of persistence or recurrence of the cyst and development of pancreatic fistulae. Three of our cases were treated in this manner.

In support of the use of internal drainage, Zaoussis [7] recently reviewed cases previously reported in which this technique had been employed and to these added five cases from the Athens Hellenic Hospital. Since that time 10 additional cases have been reported, to which we are adding 4, making a total of 118 cases in which a pancreatic cyst has been drained into the gastrointestinal tract. Surprisingly good results were obtained in 45 of a total of 52 cases in which the cyst was anastomosed to the stomach. Good results were reported in 10 of 12 cases in which cystoduodenostomies had been done and in 8 of 11 cases with cystocholecystostomies. Thirty-seven of 43 cystojejunostomies were successful (Table 1).

In our series of 12 cases (Table 2), one primary excision and two secondary excisions proved successful. External drainage by marsupialization, used in seven cases, gave good results in three cases and failed in four. Failure was due to persistence of a fistula in three cases and rupture of the cyst in the fourth. Internal drainage by anastomoses of the cyst to the duodenum, jejunum, and use of the Roux-Y principle gave good results in four cases. No failures occurred. Sphincterotomy was simultaneously performed with cystoduodenostomy in one case.

COMMENT

Many factors must be critically evaluated in the selection of an operative procedure for treatment of pancreatic cyst. These include the etiology, anatomy, and pathology involved as well as the general condition of the patient. Total excision of the cyst, if feasible, is the operation of choice. External drainage is considered of particular value in treatment of thin-walled cysts. Use of the Roux-Y principle overcomes most conceivable objections to an anastomosis of the cyst with the gastrointestinal tract; infections are decreased, nutritional complications eliminated, and technical difficulties minimized. Where total excision is deemed unwise, internal drainage, especially the Roux-Y anastomosis, appears to be giving increasingly satisfactory results.

DISCUSSION

ON PAPERS BY DRS. BERENS, BAGGENSTOSS, AND GRAY AND DRS. LAWTON AND MOSSEY

DR. HOWARD K. GRAY, Rochester, Minn.: Our interest in this particular problem arose from an experience with three patients, two of whom, interestingly enough, happened to be sisters, and all of them had lithiasis of the pancreatic duct and had had terrific attacks of pain for many years.

In all three of these cases the pancreatic duct was opened, and stones were removed, and a T-tube was left in the duct for drainage. The tube was similar to that which we have all been using for drainage of the common bile duct. The three patients were relieved immediately of their pain, and they continued symptom-free as long as the tube was in place. Frankly, we felt "we had a tiger by the tail, and we did not know when to let go," feeling that when the T-tube was removed a persistent pancreatic fistula would occur. As a matter of fact, it did not occur in any of these three patients. This experience did stimulate the thought that if patients can be relieved of the pain simply by drainage of the pancreatic duct there might be some method of establishing drainage if the normal orifice of the duct has been occluded by the various processes described by Dr. Berens.

The retrograde type of drainage has been suggested, but very little, if anything, has been written about its efficacy.

Our colleagues interested in laboratory investigation have told us that it is impossible, so far as they know, to reproduce this particular syndrome in the experimental animals. We, therefore, could not turn to the laboratory for help before trying this procedure on human beings. We desperately reached for some other evidence that might substantiate the use of such a procedure, and it was for this reason that Dr. Berens made this study, hoping that evidence of dilatation of the pancreatic duct might be found as evidence of obstruction and that this might be relieved if proper drainage could be accomplished.

Frankly, we were a little surprised that the amount of dilatation—in the number of cases in which dilatation was present—was relatively small. This was particularly discouraging, and yet I do not think it is necessarily a contraindication to the use of such a procedure in selected cases. I should like in these comments to emphasize that this is certainly not being suggested as a procedure that should be used promiscuously. It should be used only in carefully selected cases when other more commonly used procedures have failed.

An associated disease of the biliary tract was present in a rather high percentage of the cases in this series. Stones in the common bile duct and other diseases were present. It is perfectly obvious in the treatment of such a disease that one would certainly want to eradicate all the other pathologic processes that might be contributing to the formation of the inflammation in the pancreas. In some cases there is apparently nothing that will relieve the patients except, perhaps, retrograde drainage.

The fact that the excretory duct of any gland is not dilated may not necessarily mean that there is not increased intraductal pressure. You have all seen similar cases in which widespread inflammatory reaction, scar-tissue formation, fibrosis, and so forth, did not permit dilatation of the duct. This combination of pathologic features occurs commonly in situations in which the obstruction of the common bile duct is inflammatory in nature, as in cases of stones or strictures. In such cases the degree of hydrophepatosis is less than it is when the obstruction is due to extrinsic causes, such as carcinoma of the pancreas when any appreciable degree of inflammation is absent.

We hope that further study will reveal evidence that may be applied clinically for the benefit of patients who have this distressing malady.

DR. CHARLES PUESTOW, Chicago: Dr. Lawton asked me to discuss the paper. Dr. Mossey has done such an excellent job that there is not very much to add.

In the past year we have had 12 cases of pancreatic cysts and have treated most of them by various forms of internal drainage. We believe that internal drainage is the most satisfactory type of treatment because it not only shortens hospitalization but restores to the intestinal tract the digestive ferments from an organ which is already damaged and which may not be able to carry on its normal functions. If a large amount of pancreatic secretion is diverted from the body, patients often do not do well nutritionally, whereas, if these secretions are returned to the gastrointestinal tract, the convalescence is shorter and the patient will recover much more rapidly.

I should like to enumerate a few of the techniques of internal drainage and emphasize the importance of individualization in the treatment of each case.

We prefer the Roux-Y type of pancreatic cystogastrostomy with jejunojejunostomy for most retrogastric cysts. We occasionally employ pancreatic cystogastrostomy, a direct anastomosis between the anterior wall of the cyst and the posterior wall of the stomach. We have established these anastomoses both by elevation of the stomach to permit an anastomosis of the posterior wall to the anterior wall of the cyst and also by using a transgastric approach. We prefer the former method.

Many pancreatic cysts require individualization in their treatment. One of our patients had a duodenal ulcer with obstruction and a pancreatic cyst arising from the head of the pancreas and extending under the duodenum and pyloric end of the stomach. This cyst also compressed the common bile duct, producing obstructive jaundice. We were therefore faced with three distinct problems, a pancreatic cyst, a duodenal ulcer with obstruction, and obstructive jaundice. These problems were met by performing a subtotal gastric resection. The distal end of the duodenum was anastomosed to the pancreatic cyst to permit drainage of the latter into the

intestinal tract. The gall bladder was anastomosed to the duodenum to be sure of free drainage of bile into the intestines. The remaining stomach was anastomosed to the jejunum with the use of a posterior Polya technique.

Occasionally, pancreatic cysts can be resected, especially those of the retention type. One patient had such a cyst arising from the tail of the pancreas. It was retrogastric in position and lay in the cavity at the hilus of the spleen. The entire pancreatic cyst was resected with the spleen and tail of the pancreas.

I do not believe that resection of the pancreas should be performed if an extensive resection is required because we are already dealing with a badly diseased organ and do not wish to sacrifice more of it. However, when only a small portion of the tail of the pancreas needs to be removed, total extirpation of the cyst is a good procedure.

One last comment with regard to the importance of a careful diagnostic study. We had a patient just two weeks ago who presented a large cystic mass elevating the stomach upward, forward, and to the right. We had the urological department examine this patient. An intravenous pyelogram revealed a markedly dilated left kidney pelvis. An opaque medium was then injected into the left renal artery. The arteriogram demonstrated a large left cystic kidney, ruling out the diagnosis of pancreatic cyst.

Dr. James T. Priestley, Rochester, Minn.: In the past, pseudocysts of the pancreas have probably been treated more frequently by prolonged external drainage with or without marsupialization than by any other method. This form of treatment carries little risk and is usually followed by satisfactory results if drainage is continued until the cyst cavity has become completely obliterated and drainage of pancreatic juice, if this has occurred, has ceased entirely. If, for one reason or another, the external drainage is not continued for an adequate period of time, the cyst may recur. Complete removal of a pseudocyst of the pancreas is not usually advisable because of the extensive nature of the operation which this requires, as such a cyst does not possess a true epithelial-lined cyst wall. In addition, less extensive procedures will afford a good result in almost all cases. Occasionally one encounters a malignant cyst of the pancreas, and, of course, this should be removed.

My experience with internal drainage of pseudocysts of the pancreas has been rather limited, but the early results of such procedure, as reported by various authors, suggest that this may be the most satisfactory way to deal with many cysts of this type.

Dr. Arkell M. Vaughn, Chicago: I should like to emphasize further the infrequency of pseudocysts, as mentioned by Dr. Mossey. I should like to add the following information and to report on four cases in which we did operations between 1951 and 1953.

With 69,571 admissions to Cook County Hospital in 1950, there were eight pseudocysts of the pancreas due to aseptic necrosis.

In 1951, with 70,130 admissions, there were two pseudocysts.

In 1952, with 60,104 admissions, there were five pseudocysts.

In 1953, so far, none have been reported.

At Mercy Hospital, between 1946 and 1953, with approximately 80,000 admissions, there were two cases of pancreatic cysts reported. One was a pseudocyst and one was a cyst from a carcinoma of the body and tail of the pancreas.

At Cook County Hospital, there was one true cyst, which was operated on by the Roux-en-Y procedure.

At South Shore Hospital a pseudocyst was drained by marsupialization.

Another case that involved a carcinoma of the body and tail of the pancreas was likewise drained by marsupialization, and the patient eventually died, within 18 months.

With the two pseudocysts, it was out of the question to try to do primary anastomosis because the walls were too thin. In those cases we marsupialized the cysts. One cyst drained for six months and then stopped; the other drained for nine months. In both cases we did a further cholecystectomy at a later date, and to date there has been no recurrence.

Of the four cases, marsupialization was done in three, and drainage by the internal Roux-en-Y method was done in one.

Dr. Claude J. Hunt, Kansas City, Mo.: This presentation by Dr. Mossey is very practicable because from time to time these lesions are encountered. It appears that he has had more than the average experience with cystic lesions of the pancreas. They are not very common.

A similar experience with a large group of cystic lesions of this nature was presented by Dr. Charles Puestow at a recent meeting of the American College of Surgeons and no doubt later will be published in *Surgery, Gynecology, and Obstetrics.* I am sure you will find it profitable to read.

The procedure of disposal of the cyst presents a problem. Certainly it is always better to remove a cyst than to drain or short circuit it. Cysts are sometimes multiocular, and hence an anastomosis to a surrounding structure may not be adequate. Again the cyst walls are not always of sufficient texture to permit a safe anastomosis.

I relate here our experience with two very large cysts of the pancreas. One of these cases was part of a small series I presented before this Association in 1937. The most recent cyst was a very large one in an elderly lady. The tumor mass could be felt and seen distorting the abdomen. X-ray studies revealed the characteristic displacement of abdominal viscera, and a preoperative diagnosis was made of a pancreatic cyst or retroperitoneal tumor.

Abdominal exploration revealed a large cystic bluish mass showing through the gastrocolic omentum, and when the transverse colon was raised, it could be seen through the thinned-out mesocolon. Surgical exposure was through the gastrocolic route. Approach was further augmented by evacuating the fluid content of the cyst. Under this collapsed condition it was found to arise from the body-tail region of the pancreas. This segment of the pancreas was resected to include the origin of the cyst. Recovery of the patient was uneventful except for a draining pancreatic fistulous tract which persisted for many weeks.

The other case to which I refer was that of a young woman in her early 30's from whom we removed, without rupture, a pancreatic cyst which contained 1,400 cc. of fluid. A similar approach was made through the gastrocolic omentum, which is the most accessible route.

[Slide] This slide shows the size of the unruptured cyst, and the next one shows the normal pancreatic structure and the cyst wall, which is very similar to the normal epithelial structure of the pancreas. It is definitely a retention type of cyst. Recovery was uneventful in this case.

We therefore believe, when possible, that the cyst should be removed, and frequently by reducing the size of the mass or by more painstaking effort at exposure it can be accomplished. In both instances here, it first appeared that complete removal was not feasible.

One must always keep in mind that the cyst may be multiocular, and the drainage of one compartment may leave another one smaller in character to develop later. A diversion of one large segment into some adjacent viscera may present a similar future recurrence if some small unobserved cyst, or cysts, are not explored and avenues made for their drainage.

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POLYVINYL AND SILICONE COMPOUNDS AS SUBCUTANEOUS PROSTHESES

Laboratory and Clinical Investigation

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INVESTIGATIONS of foamed polyvinyl alcohol sponge, of multicellular polyvinyl chloride sponge, and of silicone compounds for use as subcutaneous prostheses in plastic surgery have been reported,* and studies of their tolerance by living tissues are being continued, as outlined below. To lend correlation with earlier reports, items from them are included here.

Deformities and abnormal contour anatomy, resulting from loss and distortion of bone, soft tissue, and cartilage, present a major problem in plastic and maxillofacial surgery, and the development of satisfactory subcutaneous prostheses is one of the greatest needs. The wide variety of substances, homogeneous, heterogeneous, foreign organic, metallic, and synthetic, that have been used to try to improve these defects is an indication that search for more satisfactory replacements should be continued. All subcutaneous prostheses should be inert in the tissue, light, resilient, have ease of workability, and should not produce tumor. Preferably, there should be prostheses of soft yielding consistency and also ones of rigid stability that would become fixed to bone.

Grindlay, Claggett, and Waugh † reported the results of implantation in experimental animals of a foamed polyvinyl alcohol sponge, which was invaded and fixed by fibrous tissue. They first became interested in this while seeking material for plumbage in thoracic surgery. During this investigation they found the sponge to be well tolerated and indicated the possibility of use around aneurysms.

Donald, Kirklin, and Grindlay [5] later used it in closure of large atrial septal defects created experimentally in dogs.

The polyvinyl alcohol surgical sponge ‡ is white, odorless, tasteless, and light, having on its cut surface the appearance of a slice of bread. Dry, the sponge is hard

Read at the Sixty-First Annual Meeting of the Western Surgical Association, Chicago, Dec. 4, 1953.

From the Department of Surgery, Plastic Surgery Service, Washington University School of Medicine.

* References 1 and 2.

† References 3 and 4.

‡ Manufactured by Ivano, Inc.; supplied through Clay-Adams Company, Inc.

and rigid. Moist, it is soft and resilient, readily resuming its original shape after being compressed, and it is quite easily cut and shaped with knife or scissors. Sterilization is by boiling 30 to 60 minutes, according to the size of piece used, and allowing it to cool without compression while hot. This sponge, in color, is available commercially for many uses.

In investigation of the possibilities of the polyvinyl alcohol sponge as a subcutaneous prosthesis, the Bar Harbor C57 mouse was used. The sponge was inserted in the subplatysma tissue, under the skin between the scapulae, with no fixation other than this pocket, and no shifting occurred except slightly in two instances.

Biopsy specimens were taken at 1, 3, 5, 6, 9, and 18-week intervals and at the end of the life span. Grossly, there was encapsulation by a thin, shiny, friable membrane, which was progressively more adherent to the sponge. On removal of this, there was a light-pink color at the periphery of the sponge, which extended deeper the longer the implant remained in place. Microscopically, there was a fibroblast capsule extending into the interstices of the sponge, with considerable collagenous-appearing material, and toward the center the interstices were clear. Vessels were noted extended into the sponge at six weeks.[1]

It is interesting that the animals did not have to be killed for examination. Wedges of skin and sponge were removed, and the defects were closed with two or three sutures through skin; all wounds healed promptly except one. In this, crusting was so severe that progressive skin loss occurred over an eight-week period, until the whole remaining implant was left exposed. But there was no evidence of acute inflammatory process; the wound was dry, without redness or swelling, and the sponge stayed in place exposed after three months; an open wound persisting over a prosthesis, in plastic surgery, would be worthless, however, no matter how long the prosthesis remained.

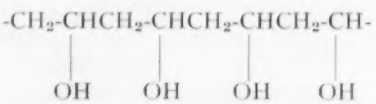
Grindlay and Waugh, in discussing the polyvinyl alcohol sponge, state that cells follow fluid and what was inert becomes living. This is an ideal concept for a perfect subcutaneous prosthesis. But there is a qualification as to the final result because of the type of tissue that extends into the interstices. Unfortunately, this new tissue is relatively avascular fibrous tissue, and resiliency and lightness are lost by this encroachment. This does not leave finally a soft area of the same resiliency as the moist sponge, but instead a rather hard area, such as fibrous tissue would produce at any time or place. Consequently, the hope for maintenance of a soft resilient consistence and feel apparently is not realized. In addition, it is not known whether the tissue within or about the sponge is more prone than other to infection, infarction, invasion by neoplasm, or injury by mechanical forces.

Because of this fibrous replacement with resultant hardness, it was obvious that a more satisfactory prosthesis would be a sponge that would retain its softness after implantation. It was thought that this desirable feature might be possible by using a multicellular sponge that remained unchanged, light and resilient, once implanted, and that would not lose the filler in its compartments into the tissues, and would not require this tissue replacement. This investigation has been done, and, with the help of the Monsanto Chemical Company, St. Louis, it was decided to use polyvinyl chloride, a nontoxic, inert, hydrocarbon in various combinations with plasticizers. A fairly satisfactory degree of pliability was obtained. However, the solid unblown

compounds were heavy and not resilient. One was implanted in six mice and was extruded in all cases in three to six weeks, but with little or no reaction. It was apparent that a sponge-like preparation would be necessary, and several multicellular "blown" compounds were then made. Two seemed satisfactory.

Implantation of these polyvinyl chloride sponges was carried out as before. One sponge remained in place two months, and on biopsy the implant was surrounded by a firm glistening capsule from which it so readily fell away as to prevent processing for sectioning. A second sponge of different preparation was less well tolerated and was extruded, so that for the time these were considered undesirable.

The basic formula of polyvinyl alcohol is as follows:



In the polyvinyl chloride sponge, Cl replaces OH, various plasticizers were added, and Celogen OT was the blowing agent to produce the foam.§

Oppenheimer, Oppenheimer, and Stout ‖ stated that Cellophane, polyethylene (both pure and commercial), and a polyvinyl chloride produce tumors in animals, chiefly of the sarcomatous type, but they have not included polyvinyl alcohol sponge in their reports. They call attention to the possibility that, whereas a tumor may appear in 1 to 2 years in a rodent, development of such a tumor might require 10 to 15 years in man.

However, the incidence of natural tumor and the variation there may be in susceptibility to tumor-producing agents are unknown in the various rodents used. It is possible that the lives of many of these mice and rats terminate with tumors in the natural course of events; it is also possible that tumor may be readily produced in them. Adequate diet control should be important in all observed series.

Grindlay and Waugh found no evidence of tumor production in dogs with polyvinyl alcohol.

It is realized that nature abhors a foreign body and that many other types of implants have given trouble, if not tumor formation, after months or years.

In our own investigation, sections of polyvinyl alcohol sponge, measuring 10 by 5 by 2 mm., or 1 cc. by volume, were implanted in 50 Bar Harbor C 57 mice. Thirty-nine of these mice had no difficulty during their normal life span of little over a year. Microscopic examination showed much the same picture as described and shown in our previous report. One mouse developed an ulcer 1.5 cm. distance from the implant eight months after implantation. A microscopic section, which included the implant and ulcer on one slide, showed what was interpreted by some observers as being a fibroma, however, with normal tissue between it and the implant. Of the 50 animals, 9 developed ulcers near the implant, but these healed spontaneously, all with permanent partial loss of the hair in this area, and microscopic sections showed only chronic inflammation and scar. These were all possibly due to implants

§ Craver, A. K.: Monsanto Chemical Company, St. Louis, personal communication to the authors.

‖ References 6 to 8.

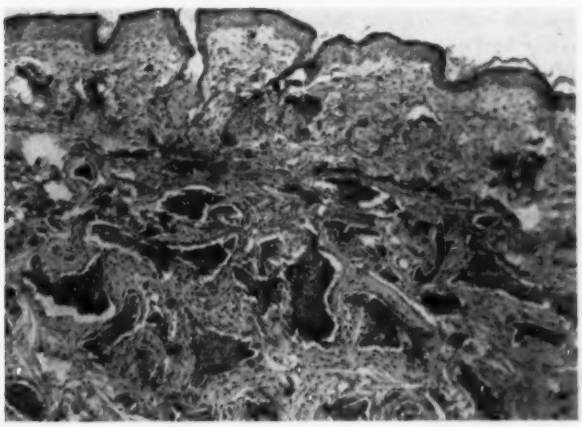


Fig. 1.—Polyvinyl alcohol sponge 12 months after implantation, at end of life cycle of mouse. There is apparently complete fibrosis of the sponge with no sign of breakdown or tumor formation, but loss of resiliency is apparent from the fibrous filling of the open interstices of the sponge. The question of resistance to trauma and infection is apparent in such a fibrous mass with so little blood vessel supply.

Fig. 2.—Showing instance of ulceration over an implant that apparently was too large, with interesting lack of inflammation about the sponge and its fibrous tissue, although the wound was open two months. Although the transplant may not be thrown off even though there is surface ulceration over it, this situation could not be classed as a successful subcutaneous prosthesis.

too large for the area. These findings indicated that tumor formation probably does not occur with polyvinyl alcohol sponge, but further work should be done before final decision is established (Figs. 1, 2, and 3).

Clinical use has been followed carefully and slowly, with application in contour defects of the face and nose, in hemiatrophy, in jaw joint resection, as well as in the applications of Grindlay and Waugh.

One article in a popular magazine suggested polyvinyl alcohol sponge to fill out breasts, but no substantial series observed over a sufficient period and no photographs of successfully persistent implants in such instances have been published.¶ This procedure, as outlined in the popular magazine, has been followed by serious trouble and unhappiness, as has been related by communications. It is apparent that the hard mass that would finally result from trying to supply missing bulk in the breasts with large amounts of such material would not give uniform success or

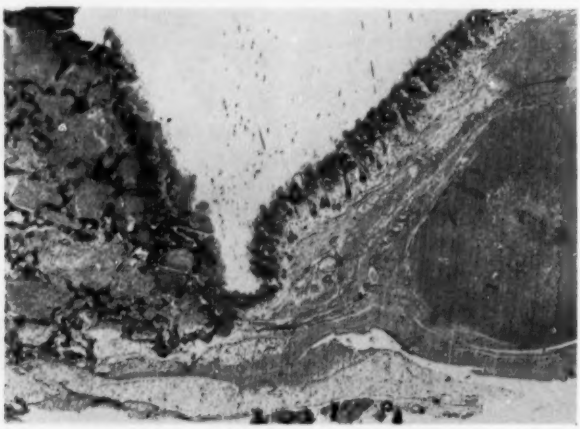


Fig. 3.—Single instance out of 50 with a tumefaction in area adjacent to implant. The enlargement was thought to be a fibroma, but normal tissue is seen between it and the implant.

enthusiasm; consequently, it may be decided for the present to forego such bulky transplants under the skin in the breast area.

It is probable that a great many things can be implanted successfully in deep pockets, with adequate surrounding soft tissue and skin covering: wood, rubber, metal, synthetics, etc. Also, in the thorax an existing cavity is being filled, and under flat flabby breast skin there is a large potential space.

But in defects of the face, met with in plastic surgery, there is likely to be scar tissue involved that has to be loosened; the circulation may be poor, motor and sensor nerves have to be avoided, and emotional expression must be retained if possible. The wound of entry must be closed and remain closed. Here it is a problem of creating a pocket often in scar, with its problematical healing.

At least, however, results have shown that small volumes of this material implanted have given a more normal feeling and do not leave the sharp edges that

¶ This popular article has been reported on unfavorably by the Bureau of Investigation of the American Medical Association.[15]

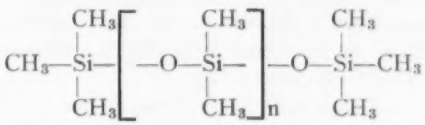
cartilage, bone, metal, and solid synthetics do in areas that are supposed to be soft. This is a valuable advantage that possibly may be gained by overlaying such sharp unnatural edges of deeper transplants with a relatively thin layer of polyvinyl alcohol sponge, and further study of the possibilities is needed. Free fascial grafts may do about the same thing.

Still better would be an inert, injectable, subcutaneous prosthesis that would stay in place, and the inert siloxane and the fluorocarbon group of compounds are being investigated for this possibility.

Silicones comprise a relatively new group of compounds that have as chief characteristics stability to extremes of heat and cold and inertness to other chemicals.# Many other unique properties give them a wide range of usefulness in industry, and in veterinarian medicine they are used as antifoamers for extreme distention in cattle, horses, and sheep. Barondes and his associates,[12] and Rowe and his co-workers [14] have published basic and inclusive papers on the reactions of these compounds in the living organism, their possible use in medicine, and their toxicology.

Because of their characteristics of inertness and stability and their failure to react with other substances, it has been thought that they might provide a suitable source of material for subcutaneous prostheses. They can be produced as volatile fluids or as hard solids, and sterilization can be done by dry heat up to 400 F., which is a good evidence of stability.

A basic molecular structure of a typical silicone is as follows:



A general term is dimethyl siloxane; the n may be as high as 2,000, with compounds of various physical properties resulting, and these compounds probably may be developed without plasticizers or elastomers.

The structure is seen to be a mixture of organic and inorganic compounds, the silica being the inorganic element that gives the stability, while the hydrocarbons give the flexibility.

Silicones have been used clinically in waterproofing skin and dressings and are applicable in many fields of medicine and surgery for use,* such as around fistulas and in preventing maceration of hands and feet adjacent to wet dressings. We are investigating the possible use of silicones in the storage of skin grafts, and they may prove useful for other stored tissues as well.

Various silicone compounds have been implanted subcutaneously experimentally, and no reaction has been noted, no tumor formation has been evident, and animals are being observed through a full life cycle for the tumor possibility. Work is under

References 10 and 11.

* References 12 and 13.

way for the development of polymers of various consistencies, with the hope that an injectable one may be developed, and also under way with another somewhat similar group, the fluorocarbons, as suggested by Barondes.

SUMMARY

Permanent, nontumor-forming, subcutaneous prostheses are a great need in plastic surgery, and it is hoped that these new compounds may be investigated and developed to supply the need.

It has been found in laboratory animals and clinically that foamed polyvinyl alcohol sponge might be a satisfactory subcutaneous prosthesis for use just under the skin, presumably without tumor formation, but tumors or breakdown might occur later in clinical use, then observed in laboratory animals, and further investigation is needed before final decision is made. Implanting large amounts of this material to fill out breast contour, as reported in a popular magazine, has resulted in a great deal of trouble in several instances, according to reports from physicians doing follow-up care on these patients.

Success in plastic surgery will depend on the availability of an adequate pocket to receive the transplant and permanent healing over it; here again, as has been repeatedly noted, the deep healing can be no better than the surface healing, and in the instance of an unsuccessful subcutaneous prosthesis the surface healing, contour, and resiliency can be no better than the deep healing.

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LEIOMYOSARCOMA OF INFERIOR VENA CAVA

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TUMORS of the inferior vena cava are a pathologic curiosity of extreme rarity. In 1950 Roussak and Heppleston,[1] in England, reported a case of leiomyosarcoma of the inferior vena cava producing obstruction of the vessel. The tumor was found at autopsy. In an exhaustive review of the literature by these authors and ourselves only two cases of primary tumors of the inferior vena cava could be found, both of which were reported in the German literature in the past century. One, a spindle-cell sarcoma containing some smooth-muscle tissue, producing complete obstruction of the vein, was reported by Perl,[2] in 1871. The other, an endothelioma in a one-year-old child, was reported by Unruh,[3] in 1896. There have been no previously reported cases of leiomyosarcoma of the inferior vena cava removed at surgery with or without survival of the patient.

REPORT OF A CASE

Mrs. A. G., a 33-year-old white woman, was admitted to Lexington Memorial Hospital on June 24, 1951, complaining of pain in the lumbar area of her back of about 18 months' duration. The pain was present constantly and was accentuated when the patient bent over. About six months previously she had consulted an orthopedist, who found a spina bifida occulta, involving the fifth lumbar and upper sacral segments. Physical therapy gave no relief, and a back support was prescribed. Spinal fusion was to be considered if the back support gave no relief. Little relief was experienced from the back support, and the patient was sent to an internist for complete examination. The internist found a mass the size of a small egg palpable superior and lateral to the umbilicus. Pressure over this area produced the pain in the back. Complete gastrointestinal x-ray examinations and oral cholecystography done at that time showed no abnormalities. The gall bladder functioned normally and contained no stones. Retrograde pyelograms showed normal kidneys, with no displacement of the kidney or ureter. The patient was advised to seek surgical consultation.

The past history was essentially negative. There had been no previous surgery or major illness.

The systemic review was nonrevealing. The patient had one child, age 9 years, born by normal delivery.

Physical examination revealed a healthy-appearing woman of 33 years in no acute distress. The head and neck were normal. The breasts were normal. The heart tones were of good quality, rhythm was regular, and no murmurs were heard. The blood pressure was 120/70. The lungs were clear throughout. Examination of the abdomen revealed a hard mass about 4 by 5 cm. in the right upper quadrant that did not move on respiration and was not tender but produced the back pain when palpated. The mass did not pulsate. Pelvic and rectal examinations were negative. There were no sensory or reflex changes in the lower extremities, and there was no edema.

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Laboratory examination showed the urine to be straw color, with a specific gravity of 1.017, acid reaction, and no albumin or sugar. The urine sediment showed 0 to 5 WBC and 1 to 3 epithelial cells per high-power field. The blood showed 4,100,000 RBC, 12.5 gm. of hemoglobin, and 5,600 WBC, with 64% segmented forms, 35% lymphocytes, and 1% monocytes. The blood nonprotein nitrogen was 24 mg. and the blood sugar was 130 mg. per 100 cc.

X-ray examination of the chest showed no abnormalities.

A diagnosis of retroperitoneal tumor was made, and exploration was advised.

On June 25, 1951, surgical exploration was done under spinal and intravenous thiopental (Pentothal) sodium anesthesia. With the patient in the right lateral nephrectomy position, an approach was made through a transverse incision in the right flank. The right kidney was found to be normal, as was the right ureter. Lying medial and somewhat inferior to the right kidney, a tumor approximately 3 by 5 cm. was found, which seemed well encapsulated laterally and unattached. On further examination the medial aspect of the tumor seemed to be attached to the inferior vena cava. At this point, the peritoneum was opened and the abdomen was explored. The abdominal viscera were entirely normal. No aortic nodes were involved, and there seemed to be no evidence of spread of the tumor. By careful blunt dissection, an attempt was made to

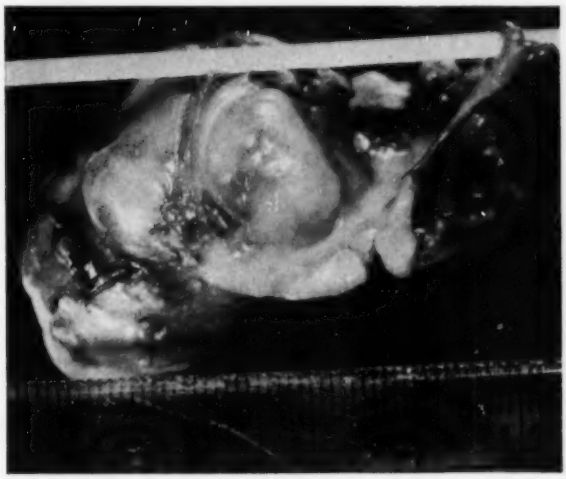

Fig. 1.—Leiomyosarcoma arising from the wall of the inferior vena cava.

separate the tumor from the wall of the vein, but it then became evident that the growth was arising from the wall of the inferior vena cava. During the dissection the vena cava was inadvertently torn into. The vena cava was then resected from a point just inferior to the renal veins down to the iliac veins. The ends of the vessel were transfixed and securely ligated with 00 nonabsorbable surgical (silk) sutures. The wound was closed with 0 chromic absorbable surgical (gut) sutures, and the skin was closed with silk.

The patient was placed in moderate Trendelenburg position in bed, and on the second postoperative day she was taking fluids by mouth and had no complaints. On the fifth postoperative day there was some tenderness in the calf of both legs, with suggestive Homans' sign and slight swelling of the ankles. Bishydroxycoumarin (Dicumarol) therapy was started, and the prothrombin time was depressed to 30% of normal activity for a period of seven days. The patient was then permitted slowly to stand up and began walking. There was no fear of embolism. Swelling of the ankles did not reappear, and the patient was dismissed on July 20, 1951, in good condition.

Pathologist's Report.—Gross Pathology: The tissue submitted for examination consists of a portion of the vena cava with attached tumor (Fig. 1). Present in the wall of the vena cava and extending into the lumen one may recognize a tumor mass which measures 6 by 3 by 3 cm.

This tumor mass is rather solid and white in color and is sectioned with moderate resistance. The cut surface of the tumor is homogeneous, except for a few areas which appear necrotic. The neoplasm appears to have its origin in the wall of the vena cava.

Histopathology: Multiple sections of tissue reviewed display the features of a malignant neoplasm. This neoplasm features cells which vary in size, shape, and staining qualities. Mitotic figures are present, and a disorderly growth pattern is noted. The cells are spindle to fusiform in shape and are growing in the pattern of smooth muscle. The lining of the vena cava has been interrupted at one point. Differential stains support the impression of smooth-muscle origin (Fig. 2).

Fig. 2.—Histopathology specimen. Differential stains showed this tumor to be of smooth-muscle origin.

Diagnosis: Leiomyosarcoma of the inferior vena cava.

Further Course.—The patient was given 4,800 r of deep x-ray therapy over a period of three and one-half weeks, distributed evenly over three ports.

The patient was checked at frequent intervals for the next 16 months and remained free of back pain. X-ray examinations of the chest at monthly intervals were all negative, and there was no local or distant evidence of recurrence.

The patient remained well until Oct. 15, 1952, when she again noticed the same back pain on bending. Examination of the patient at that time revealed a small palpable mass in approximately the same location as the original tumor. There was still no evidence of distant spread, and exploration was again done through a transverse incision in the right flank. A tumor

approximately 3 by 3 cm. was found, involving the inferior wall of the right renal vein. There were no aortic nodes, and, again, the peritoneum was opened and the abdominal viscera were found to be normal. The left kidney was palpated and found to be normal. The right renal artery was divided and ligated flush with the aorta. The inferior vena cava was resected at an angle, leaving a channel for the left renal vein, and the right kidney and the tumor were excised. One cubic centimeter of heparin (Depo-Solution Heparin) sodium was given during the surgery.

Grossly, the tumor measured 4.5 by 3 by 2.5 cm., and the cut surface appeared similar to that of the primary tumor, removed 16 months previously (Fig. 3.). The tumor was confined to the renal vein, and there was no involvement of the kidney itself. Microscopically, the tumor was identical to the leiomyosarcoma removed previously.

Postoperatively the patient was given bishydroxycoumarin sufficient to depress the prothrombin time to 25% of normal activity for a period of nine days. It was feared that the venous

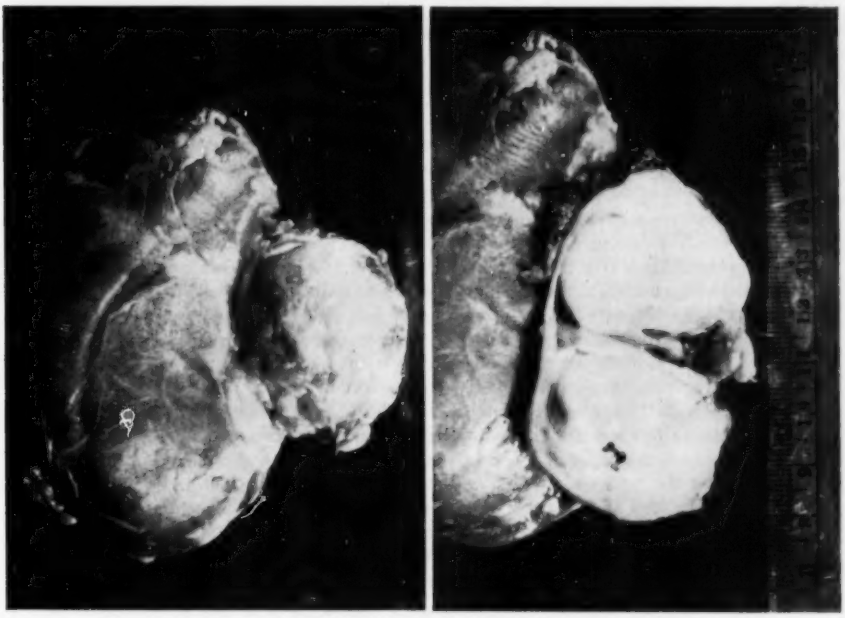

Fig. 3.—Recurrence 16 months later, in right renal vein.

channel to the left renal vein might thrombose. The patient had an uneventful recovery and was dismissed from the hospital in excellent condition, on Nov. 4, 1952.

The patient remained well until Nov. 1, 1953, when she again began having pain in her back and cramping pains in the lower abdomen. Examination three weeks later, when she returned from Honolulu, revealed another hard mass in the same area, somewhat smaller than before. X-rays of the lumbar spine and chest were negative, and there was no evidence of distant spread.

On Nov. 19, 1953, exploration was again done through the same approach, and two tumor masses, one 2 cm. and the other 3 cm. in diameter, were found lying on the body of the second lumbar vertebra and overlying the aorta. The tumor was firmly attached to the stump of the right renal artery. The tumor was not attached to the stump of the vena cava. The mass was excised, and the aorta was sutured at the point of attachment to the stump of the right renal artery. A radium pack, consisting of 20 mg. of radium needles encased in 0.6 mm. of platinum and 1 mm. of lead and covered with rubber, was placed in the bed of the tumor and was removed in 92 hours.

Recovery has been uneventful, and the patient is again relieved of her pain.

SUMMARY

A case of leiomyosarcoma arising in the wall of the inferior vena cava, surgically removed, is reported. A recurrence involving the right renal vein was likewise removed, as was a second recurrence, which did not involve the vein.

We believe this to be the only reported case of a leiomyosarcoma arising in the wall of the vena cava, removed at surgery.

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DISCUSSION

DR. CLAUDE J. HUNT, Kansas City, Mo.: I am very grateful to the committee for permitting Dr. Cope to present, before this Association, this very unusual case. As was recorded, there are few or no such cases found in the literature, especially none that have been found at operation.

Dr. Cope deserves a great deal of credit for his persistence in the management of this case and for the very skillful operative procedures he has done. It demonstrates the technical skill of men of his age that was not present in many of us years ago. It demonstrates the progress of surgery and the surgical approach that is now being made in treating many patients with a relative degree of success that in former times were not given the opportunity of any palliative relief by surgical extirpation of their lesions. Dr. Cope has done three major operations, and the patient has recovered from all three. The interesting thing is that although there was an obstruction of the vena cava there has been no appreciable edema. In fact, there has been no edema at all, because I have seen this patient on a number of occasions. The reason that there is no edema is that this is a slow occluding lesion of the vena cava and during the passage of time collaterals have developed; consequently, after its extirpation there were plenty of accessory channels for the return of blood flow without the production of edema. This is quite in contrast to the situation of ligation of the inferior vena cava for an embolus resulting from a phlebothrombosis. In such a case there has been no appreciable time for collaterals to develop and there is for a definite period of time a considerable amount of edema after ligation. However, with the passage of time edema becomes less and less as collaterals develop.

We have, on another occasion, excised the entire abdominal vena cava in association with a retroperitoneal tumor in an old woman. This patient made a good recovery, and in her case there was no edema of the lower extremities, because she, like this patient of Dr. Cope's, had built up lateral circulation over a long period of time. This case represented extrinsic pressure upon the abdominal vena cava, while in the instance presented here by Dr. Cope there was an occlusion due to a lesion of the abdominal vena cava. The result in each instance was the establishment of abundant venous collaterals.

Although this is a presentation of one case, it is so unusual that it has been well worth while to have it presented, and it will be very interesting to the Association, because it wil become a part of the scientific procedures, which will be in a bound volume.

I have been interested through the years in looking over the proceedings of the Western Surgical Association, and I think that if one reviews the volumes over a period of years he will find every phase of surgery, sometime or another, has been discussed at the scientific meetings of the Association. This demonstrates the splendid judgment of the program committee in seeing that these various scientific surgical subjects are sometime or another presented before the Association. They thus become the scientific record of the Association and are excellent for reference work. Such complete discussions of all phases of surgery has made the Western Surgical Association an outstanding organization.

SURGICAL MANAGEMENT OF ULCERATIVE STASIS DISEASE OF THE LOWER EXTREMITIES

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THE OUTSTANDING features of ulcerative stasis disease as it affects the lower extremities are the tendency to swell, the development of incompetent or varicose superficial veins, and the changes which occur in the skin and subcutaneous tissue of the stasis areas on the medial and lateral aspects of the lower third of the leg. The edema is ascribable to lymphatic vessel disease and to venous insufficiency, either or both factors being present in varying degrees in individual cases. Unless there have occurred repeated episodes of inflammation, the lymphatic element ordinarily diminishes with time. It is at its greatest severity in the early period following the acute thrombophlebitis to which it is an accessory. The venous element of the stasis arises either from permanent occlusion of the deep veins of the extremity or to the tendency for reflux venous flow in a vien which has been rendered valveless by the original infection. The varicose veins which are characteristic of stasis disease appear in response to the general increase in the venous bed and pressure secondary to deep vein disease of the legs. They are the subcutaneous component of the developing collateral venous system. Inasmuch as these veins are unsupported by fascia and muscle pressure, they quickly dilate beyond the ability of their valves to remain competent, and they become reflux venous channels.

It is pertinent also to consider, as a part of the general subject of stasis disease, primary varicose veins. It is generally accepted that the underlying cause of varicose veins which appear in the absence of any deep vein disease is an intrinsic defect in the vein wall of the saphenous system itself, in addition to occupational factors which may keep a patient standing for long periods of time.

The skin changes which appear in stasis disease or in primary varicose veins are characteristically located in the same areas. These areas are the medial aspect of the ankle above the malleolus in the course of the long saphenous vein system and

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the lateral aspect at about the same level in relation to the lesser saphenous system. To explain this uniformity of the affected area, it must be assumed that some peculiarity exists in the structural anatomy at these points or in the pressure relationships within the veins, which may be responsible for the skin and subcutaneous tissue changes. If such a peculiarity can be worked out, a method might become available for the permanent healing of stasis ulceration as it occurs as a feature of deep vein disease. The most workable hypothesis as to the cause of the routine manner in which ulcers appear in these areas concerns the presence here of the greatest number of veins communicating between the deep venous system and the superficial channels. This reasoning has been applied by Linton [1] in developing a method of individually ligating these branches, which has been satisfactory to an unprecedented degree in producing long-term good results. The presence of these incompetent perforating veins has been considered in a number of attempts to obtain relief of venous stasis through the application of uniform external pressure. Their importance has been especially emphasized by Scott and Radakovitch [2] and Scott.[3]

Other than the presence of these perforating veins in the area of ulceration the character of the tissue changes which precede the breakdown of the skin must be considered. Changes far enough advanced to make a return to normal unlikely must be recognized as a factor determining the need for total eradication of the diseased skin and subcutaneous tissues of the area. The need for excision because of these changes has been noted by Blalock and Ray,[4] while others have considered the removal of the saphenous veins together with the immediately surrounding fibrotic tissue to be sufficient.[5]

The method of surgical treatment which has seemed to us to be most likely to provide long-term relief is that which includes removal of all the damaged skin and subcutaneous tissue together with the underlying fascia, the involved saphenous system, and the local perforating veins. The seemingly irreversible character of the tissue changes locally seems to warrant this radical approach. With application of this form of management for a period of time which may be significant, the clinical results obtained together with certain observations on the secondary stasis changes and the anatomy of the venous perforators will be described.

DETAILS OF TREATMENT

The preoperative management follows conventional methods and is directed to elimination of infection about the ulcerated area and complete control of the edema of the leg and foot. Reepithelialization of the ulcer has not been considered necessary. Bed rest with elevation of the limb, intermittent application of moist dressings to the ulcerated area, and parenteral administration of antibiotic therapy are utilized. The extent and severity of the cutaneous and subcutaneous fibrosis is determined by palpation after local inflammation has subsided. When the ulceration is superficial and not of long standing and the tissue changes are minimal, ligation and complete stripping of the involved saphenous system may be judged to be sufficient for permanent healing of the ulcer, and no further operative treatment is planned.

The majority of patients in our series, however, have had recurrent ulcerations for years, and many have had previous ligations and strippings of veins without satisfactory results. In these cases at surgery the ulcer area is excised widely enough to reach good skin. The subcutaneous tissue which is densely fibrosed and often

contains small abscess-like areas filled with cloudy fluid is removed in a single tissue block attached to the skin superficially, taking with it all of the deep fascia adherent to its undersurface. From two to seven veins of major size have been found in our cases perforating the fascia in this area to communicate between the subcutaneous veins and the deep veins. These are clamped and ligated. A split-thickness skin graft, taken usually from the anterior aspect of the same thigh and having a thickness of 0.012 to 0.016 in., is used to cover the defect after complete hemostasis has been obtained. Small V-shaped perforations are made by short snips with the scissors over the entire surface of the graft after it has been sutured in place. These perforations are evenly spaced a little over 1 cm. apart. In addition to these perforations the skin graft is sutured to the muscle bed over the entire area with fine plastic suture material, the intervals between these stitches being approximately the same as between the perforations. As the grafted site is dressed with moist saline gauze and wrapped with elastic bandage, one to three very small urethral catheters are included in the dressings for the postoperative instillation of 0.2% neomycin solution. The ends of these catheters are incorporated in the substance of the moist gauze in relation to the graft. These precautions are without a doubt unusual and may not be essential in each case. However, their application has, in our hands, provided for complete freedom from any significant loss of graft. They have not presented any disadvantages. The perforations heal without leaving noticeable marks, and the sutures to the bed have only the disadvantage of being somewhat difficult to remove without leaving the suture loop behind.

Since the ligation and stripping and this radical excision are done at the same operation, the patients are deprived of the supposed advantage of ambulation on the day of surgery. The fact that they must be immobilized for the benefit of graft healing for a period of 7 to 10 days has not resulted in any of the vascular complications which were at first feared. The sutures at the base of the graft are removed on about the fifth day. The sutures around the edge of the graft are left in until the 10th day. Earlier removal permits shrinkage of the graft from the bed edges. When the graft has healed completely, at about this time, a program of graded ambulation is instituted.

LOCAL ANATOMY AND PATHOLOGIC CHANGES IN THE STASIS AREA

Complete removal of the stasis area in one block from the skin surface through the deep fascia has provided an opportunity to observe the pathologic anatomy and tissue changes which are present. During the surgical procedure two to seven venous pathways have been noted, passing through the fascia, between the subcutaneous tissue and the subfascial vein. Within the substance of the excised tissue there are large, thin-walled, tortuous venous channels which tunnel the densely fibrous tissue. The number and size of these veins diminishes strikingly at the border of the stasis area so that although there are many veins within the removed specimen, at the edge of the excision only a few veins are encountered during the procedure. When the specimen is sectioned vertically, the cut surface is fibrous and wet with liquid fat. Cavities from 2 to 8 mm. filled with this fluid are seen. Cultures of this material are sterile unless the test is made close to the ulceration of the skin.

Attempts have been made to demonstrate by phlebography the presence of this concentration of subcutaneous veins and of communicating veins. Figure 1 shows the

lateral and anteroposterior x-rays taken after injection of a superficial venous channel on the dorsum of the foot. This illustration is from the case of a 35-year-old man who suffered an acute thrombophlebitis of the left leg in 1946. An ulcer on the medial aspect of the left leg appeared in 1948 and was treated two years later by excision of the type described with application of the split-thickness skin graft. This graft healed well and has remained so to date. The application of the graft was preceded by ligation and stripping of the long saphenous system. In 1952, two years after the radical treatment of the ulcer on the medial aspect of the leg, cutaneous ulceration appeared on the lateral surface of the same extremity. Examination showed marked stasis change in the area superior to the lateral malleolus, in the center of which a deep ulcer was present. The phlebograms show the presence of the large lesser saphenous vein, which was also demonstrable on physical examina-

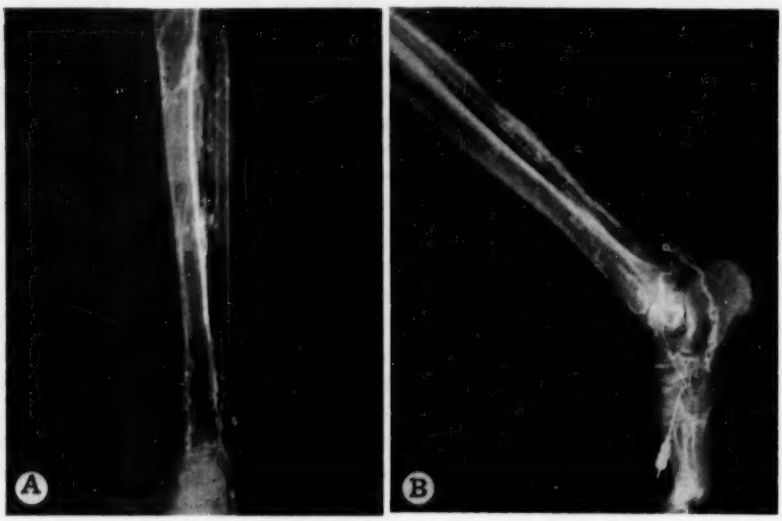

Fig. 1.—Anteroposterior (*A*) and lateral (*B*) phlebograms in patient having long-standing stasis disease and ulcer superior to lateral malleolus (lead marker).

tion, and the many tortuous veins in the subcutaneous tissue in the lateral stasis area. Interpretation as to the venous layer in any such visualization is difficult. It is thought, however, that in the anterior-posterior view immediately in the region of the ulcer, which is marked by the left marker, there are three perforating collaterals. During the excision of the stasis area, four large channels perforating the deep fascia were encountered. This patient, who now has a graft on each of the surfaces of his left lower extremity, has been free of recurrence in either area.

Figure 2 is the lateral view of the phlebogram of the right lower extremity of a 29-year-old white man who had a severe deep thrombophlebitis of the right lower extremity in 1949. Recurrent ulcerations and deepening pigmentation had been present, despite long saphenous-vein ligation and stripping, from 1950 until the time that he was seen in January, 1953. The phlebogram demonstrated the concentration of tortuous dilated channels in the stasis area above the malleolus. The dimensional

Fig. 2.—Lateral phlebogram in 29-year-old man having stasis disease of four years' duration. The large number of venous channels seen were found in the subcutaneous tissue when the area was excised.

Fig. 3.—Photograph of a stasis specimen showing pigmented and ulcerated superficial surface. The cut surfaces of this specimen showed sterile "abscesses," extensive fibrosis incorporating large venous channels.

Fig. 4.—Undersurface of specimen illustrated in Figure 3. Upper arrow points out a tortuous subfascial channel communicating frequently with the subcutaneous veins above the fascia. Lower arrow indicates another perforating vein.

Fig. 5.—Photograph taken 14 days postoperatively, showing grafted area. The crusts over points of perforations remain.

limitations of this phlebogram do not permit any accurate impression as to the number or presence of perforating veins. At the time of excision of this ulcer-bearing stasis area, however, one very large such perforator was found almost directly in relationship with the ulcer. Figure 3 shows the external appearance of the removed specimen, including the ulcer. Figure 4 shows its undersurface. The upper arrow indicates a subfascial channel leading to the ulcer site, and the lower arrow shows a large perforating vein which connected the superficial and deep systems. Figure 5 is a photograph of the graft taken during the early postoperative period. Healing continued satisfactorily, and the graft has remained pliable and intact to date.

CLINICAL RESULTS

Fifty-four grafts which have been applied by this method in 41 patients have been followed for periods up to five years. The results are summarized in Table 1.

TABLE 1.—*Clinical Results*

	Grafts, No.	Patients, No.
Failures *	21	10
Successful †	33	31
Total	54	41

* Seven grafts failed in one patient; three in another patient, and two in a third patient.
† Two grafts were successful in each of two patients.

TABLE 2.—*Results in Relation to Time*

	Grafts, No.	Time
Failed	18	Between 2 and 6 mo.
	3	After 6 mo.
Successful	2	Followed 5½ yr.
	6	Followed more than 3 yr.
	12	Followed more than 2 yr.
	13	Followed 6 to 24 mo.

Thirty-three of these were successful in 31 patients, all having follow-up periods in excess of six months. Of the 21 failures in 10 patients, 12 occurred in 3 patients and 7 unsuccessful grafts were attempted in 1 patient. When failure occurred, the time interval between operation and reulceration was usually short. The time of failures and length of observation of successful cases is shown in Table 2 (Fig. 6).

Recurrence of ulcer was most frequently at a site involving the skin immediately bordering on the graft edge. In these instances it is felt that insufficient excision had been done. Reoperation, taking a larger area, has occasionally resulted in success. Ulceration of the graft itself was encountered infrequently and was almost confined to the area of the malleolus when it was included in the graft site (Fig. 7). This site of grafting was, however, frequently stable, and we believe the area must be excised if the changes present require it (Fig. 8).

The most significant single factor in recurrences was failure to control edema in the leg after the surgical treatment is over and the graft completely healed (Table 3). The immediate postoperative period is routinely followed by very gradual

Fig. 6.—Long-term follow-up photograph taken 40 months after surgery. Graft shown is on medial stasis area. Fissuring is due to folding under pressure dressing. Some edema has been present in this case since surgery. Ridges in leg indicate degree.

Fig. 7.—Example of a failing graft, showing breakdown over tip of medial malleolus.

ambulation. This is controlled easily because the patient is either still in the hospital or is being watched closely as an outpatient. The later return to wider activity is graded most carefully. Routine periods of elevation of the extremity are required to break the day into several parts. Heavy elastic support is used from toes to knee, and it is only an exceptional good result which does not require the permanent use of the stocking.

It is during the period of late graded ambulation that patient cooperation is sometimes lost, with resulting increasing edema and recurrence. Our impression was that private patients were less often failures in edema control. Examination of our results, however, did not show this tendency to be significant.

Fig. 8.—Small successful graft over medial malleolus. This graft has been followed now for a period of two years without recurrence.

TABLE 3.—*Results in Relation to Edema*

Grafts	Postoperative Control of Edema	
	Good	Poor
Successful (33 in 31 patients)	27	6
Failures (21 in 10 patients)	3	18

COMMENT

It is difficult to tell from the literature the origin of this method of treatment of stasis disease of the lower extremities. We know that the procedure has been widely followed, but reports of clinical experience are meager. It accomplishes certain aims in the treatment of stasis disease which we believe to be important. The diseased tissue in which the damage is most frequently manifestly irreparable is completely removed. The incompetent communicating veins in the stasis area are likewise completely ablated, and combining the procedure with ligation and stripping of the long or short or both saphenous systems gives the best relief of reflux venous flow, at least in the superficial system. That failures occur is evident from Table 1. It will also be noted that in most instances the failures were present in patients who

had the greatest degree of persistent edema which was controlled with difficulty. Some salvage in these cases can undoubtedly be obtained through the ligation of the femoral vein or popliteal vein, as recommended by Linton, Ochsner, and deTakats. These techniques have not been applied in any of the cases of this series.

SUMMARY

The uniformity of location of serious stasis changes leading to ulceration of the lower extremity suggests an anatomical peculiarity in the regions. The factor responsible is probably the presence of incompetent perforating veins between the superficial and deep circulations in this area.

Severe and often irreversible changes occur in the skin and subcutaneous tissue of the stasis area accompanying the ulcer.

Removal of both factors by radical excision of the stasis area and replacement by split-thickness skin graft has been accomplished in 41 patients whose response to the treatment has been followed for periods up to five years.

Clinical results are acceptable in this stubborn disease, but the not infrequent failures show the need of additional armamentaria which may well be femoral or popliteal vein ligation.

DISCUSSION

Dr. Alexander Blain, Detroit: It is a privilege to have heard this paper of Dr. Julian's, and I feel that he and his group have made a real contribution in bringing this subject to the attention of this meeting.

Those of us who are interested in the problem see a tremendous number of cases that have had one type of operation or another, but these patients still have the same basic difficulty—edema, eczema, and ulceration.

The key to the treatment of the post-thrombophlebitic syndrome is the control of the swelling itself. No operative procedure can be expected to result in success if this factor is forgotten.

At the vascular clinic in the University Hospital, Ann Arbor, many of the patients came from the northern peninsula of Michigan, and no matter what we did for them, if they disappeared from our observation for a year or two and were not seen by an interested physician up north, they would return without adequate control of their edema and with recurrent ulcerations. This same problem was observed in the outpatient clinic at The Johns Hopkins Hospital.

On the other hand, at the Blain Clinic, in Detroit, where most of our patients from nearby come and can be followed regularly over a period of years, we have little trouble with swelling because we can control the edema with elastic stockings.

It should be emphasized that elastic stocking must be fitted to the normal leg, or, if there is not one, to the swollen leg only when the edema is minimal. The stockings must be of heavy material, must cover the heel, and must have a two-way stretch. They can be made of either cotton or nylon, and there is no necessity for them to extend above the knee. In some cases in which one elastic stocking will not control the edema, then the patients should wear two, one right over the other. In rare cases, one will have to supplement two such stockings for a while with additional Ace bandages.

I do not believe that Dr. Julian meant to imply that excision of the stasis areas is to be considered unless there is an actual open ulcer present. His observation that the location of these ulcers is the site of the greatest number of communicating veins above the malleoli is interesting. In our past experience, however, excision of such ulcers with grafting would be followed in about a year by recurrent ulceration at the same site, even though the excision included all perforating veins. In recent years, our recurrence rate following this operation has been significantly reduced because of careful prevention of edema after operation. This same fact is apparent in Dr. Julian's patients.

Dr. John H. Olwin, Chicago: I think Drs. Julian, Dye, and Schneewind are to be congratulated on the treatment of a very tedious and often discouraging condition.

There are just two points that I should like to add. The bed which receives this graft is hardly ideal, and we have found that we have a higher incidence of viable grafts if we splint these legs postoperatively with a plaster boot. This is left on for a week to three weeks, minimizing and almost reducing to zero the movement of the leg, so that the graft has a better chance of remaining viable.

The second point, as Dr. Julian has mentioned, is that the control of edema is a very important item. Now, in addition to this, and almost with the same mechanics, the graft can and should be protected from trauma. Any trauma injures these cells, which are not too rugged anyway, and we have found that the use of a ¼ in. (0.6 cm.) sponge-rubber protector overlapping the edges of the graft area for a few centimeters, under either an elastic bandage or elastic stocking, is very helpful in protecting these grafts both from edema and from trauma (both minor and major) to which the lesions are constantly subjected.

Dr. Eslie Asbury, Cincinnati, Ohio: I think we are all agreed—the essayists and everyone else who has done a lot of work in this type of case—that the graft adds a great deal to the permanence of a possible cure. I think that the two men who spoke are agreed that nearly all of these persons are permanently crippled, and the thing we must bear in mind is that these patients have extensive damage to the tissues due to the induration and thrombophlebitis; it is not that they have an ulcer in just one spot, but they have potential trouble from the knee down, and I think that no amount of surgery and grafts can bring these advanced type of cases back to normal.

How are we going to combat the edema? This is the critical question. I have been working with this thing for years, and I have never been able to get a stocking that would control this edema. I mean the stockings will not continue to fit—even one, or two, or three. The only thing I think that really will do the job—and the patient has to be taught it—is a properly applied bandage. I believe that it does help to put stockings on over the bandages to hold them in place.

Dr. Harry B. Zimmerman, St. Paul: All the speakers have stressed the idea of stopping the edema by properly applied pressure. The last speaker is quite right. It is very, very difficult to get an elastic stocking to fit with the same pressure over the ulcer as over the normal leg.

There is available—not to surgeons or physicians, but to chiropodists—a felt material that comes in large sheets, sized on one side with Latex and a zinc-oxide-material like adhesive plaster. This material is about a ¼ in. thick, and if one cuts out a pattern of the area that is to be covered and applies pressure (and if it is not thick enough, put on two or three) and then puts the elastic stocking over that and leaves it on, the edema is quite easily controlled. That material is quite a lifesaver—just a thick piece of felt, sized on one side. The chiropodists use it to protect bunions and corns. It comes in large sheets.

Dr. Eugene A. Osius, Detroit: I do not want to prolong this discussion too much, but I have been interested in this subject for a good many years. As Dr. Julian says, to the group that is interested in vascular subjects, this subject stands foremost among the list of disturbing entities, both to the physician and to the patient.

I was very much impressed with Dr. Julian's results and his method of handling them, but I am quite sure that it is not just as simple as he was able to explain here in the given length of time he had, and that there is a good deal more to it than you have been able to hear from him. In other words, there is the preparation of the patient beforehand, the meticulous follow-up, and the constant care that is necessary.

As Drs. Zimmerman and Asbury have said, these patients are cripples that stay with you, and they have crippled limbs from the time they are born until they die.

I should like to make two simple points. One notes the frequent association of fungus infection in these patients. This must be treated as a complicating entity, or failure results.

The other point concerns the simple basic things that we all learned as little boys, and that is that soap and water is a wonderful thing and should be used. By that I mean we must stress and instruct the patient in strict personal hygiene. If you consider, the patients with the worst ulcers are not the patients who come from the so-called "good strata" of society but, rather, are those who are careless about their hygiene, or workers who can not help being dirty because of their occupations.

These are two important points.

The problem is not one particular type of treatment but a regimen or a general scheme of education, together with all of the other things that have been stressed.

DR. ORMAND C. JULIAN, Chicago: I should like to add one or two brief remarks.

First of all, concerning open ulcer, which was mentioned by Dr. Blain, we have gained sufficient confidence in this method to have applied it in a number of cases in which there was not yet an open ulcer. These cases present a dense pancake of severe stasis change, in which all of the other pathology is present but the skin is still intact. Perhaps this will prove to be something that is worth while.

As to the matter of bandages, I agree very heartily with Drs. Asbury and Zimmerman that there is not too much confidence to be placed in stockings. Sometimes we use stockings and bandages, but was put the bandages on top of the stockings rather than the other way around.

I suppose if this whole thing were to be characterized, Dr. Osius—who has a good story about almost everything—has done so. He said that he felt the one thing that characterizes vascular surgery is that it is carried on by a group of persons who are willing to put forth a tremendous effort to gain very, very little.

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PHEOCHROMOCYTOMA

Clinical Aspects and Surgical Results

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PHEOCHROMOCYTOMA, while relatively uncommon, is the most frequently encountered surgical lesion known to arise from the medulla of the adrenal glands. Although this tumor may be nonfunctioning and cause no alteration in blood pressure, usually it liberates pressor substances which produce either paroxysmal or sustained hypertension or a combination of the two. This tumor is not a common cause of hypertension, but if the diagnosis is made relatively early during the course of the tumor, complete relief may be anticipated after surgical removal in virtually all cases.

The present study, which is based on a group of 25 patients seen between January, 1944, and February, 1952, each of whom had pheochromocytoma, was undertaken primarily to evaluate results after surgical removal of tumors of this type. Unfortunately, the diagnosis of pheochromocytoma is not easy, and some patients may harbor this type of tumor for many years before it is recognized. Because of this fact, brief comments will be made relative to clinical recognition and diagnosis of pheochromocytoma. In addition, important pathologic characteristics and considerations of significance in the surgical treatment and postoperative care of patients who have such a tumor will be discussed.

CLASSIFICATION OF HYPERTENSIVE STATE

The grouping of patients with hypertension caused by pheochromocytoma into those who have paroxysmal hypertension and those who have sustained hypertension has been largely arbitrary.

Patients with labile hypertension frequently have periods of elevated blood pressure which may be paroxysmal. In contrast, the intermittent release of the pressor substance from a pheochromocytoma produces the paroxysmal hypertension together with a group of signs and symptoms which are designated as an attack and which will be described more fully later.

For the most part in this study, patients with paroxysmal hypertension who had experienced attacks during a period of several years tended to show hypertensive

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changes on examination of the ocular fundi or with a sphygmomanometer, or both, whereas those patients who had attacks for several months only revealed normal ocular fundi and normal blood pressure between the attacks. In this group of 14 patients with paroxysmal hypertension, 8 showed evidence of hypertensive changes, while 6 had normal ocular fundi and normal blood pressure between attacks.

Of 11 patients who experienced sustained hypertension as a result of pheochromocytoma, 10 had hypertensive changes in the ocular fundi. These changes grouped according to the Wagener-Keith classification were considered to be those of hypertension Group 4 in three patients, Group 3 in four patients, Group 2 in one patient, and Group 1 in two patients. The blood pressure in these patients was variable from time to time, but in all but one patient the systolic pressure was more than 200 mm. Hg and the diastolic pressure was more than 130 mm. on one or more occasions.

CLINICAL ASPECTS

If paroxysmal hypertension is caused by pheochromocytoma, the patient experiences attacks which usually occur every day or so but which may occur only once in two months. Commonly, these attacks last 10 or 15 minutes but may persist for as long as a week. They are characterized in addition to hypertension by one or usually more of the following symptoms: headache, vertigo, anxiety, sweating, flushing or pallor of the face, dyspnea, pain in the chest or abdomen, "pounding" in the epigastrium, and a feeling of warmth, nausea, vomiting, weakness, and tremor. Headache, usually severe and generalized, is the commonest presenting symptom and is almost invariably present. One or more of the vasomotor phenomena just mentioned and perspiration also usually occur. In all but one patient studied during an attack, the blood pressure, which between attacks was normal, rose to more than 200 mm. Hg systolic and 110 mm. diastolic. Although the ages of the 14 patients who had paroxysmal hypertension varied considerably, the average was 43 years.

The usual laboratory studies reveal essentially normal findings in the patient who has paroxysmal hypertension caused by pheochromocytoma. The basal metabolic rate was determined in 13 of the 14 patients in this group and was elevated to more than +10% in only 3 cases. Occasionally tolerance for glucose may be decreased.

The average age of the 11 patients who experienced sustained hypertension as a result of pheochromocytoma was 29 years. One should always consider pheochromocytoma as a possible cause of persistent hypertension when it occurs in a young person. The patient who has sustained hypertension caused by pheochromocytoma at times may present a clinical picture which is identical with that of the patient who has essential hypertension. This fact, of course, adds difficulty to the differential diagnosis of these two conditions. Some patients with sustained hypertension may have attacks similar to those experienced by patients who have only paroxysmal hypertension during which the blood pressure rises to even higher levels. Headache, weakness, profuse perspiration, and palpitation are the commonest symptoms. Symptoms dependent on secondary cardiovascular changes, such as loss of vision or nocturnal dyspnea, may be present. A palpable mass was noted in only two patients, both of whom had malignant tumors. The basal metabolic rate of all but one patient with sustained hypertension due to pheochromocytoma was more than +10%, the highest figure being 101% and the average being +49%. Clinical diabetes or elevation of fasting blood sugar is not uncommon. Occasionally bilateral

tumors may occur in patients with either paroxysmal or sustained hypertension. Furthermore, such tumors have been found in two and three members of the same families.[1]

PHARMACOLOGIC TESTS

Fortunately, certain drugs are useful in the diagnosis of pheochromocytoma. These are extremely helpful, not only for purposes of screening relatively large numbers of patients who might have pheochromocytoma but also for the purpose of establishing a relatively definite diagnosis. In general, two types of drugs are employed. For patients suspected of having pheochromocytomas associated with paroxysmal hypertension, histamine,[2] tetraethylammonium chloride,[3] and methacholine (Mecholyl) chloride [4] are the drugs used, as they will elevate the blood pressure and produce the other signs and symptoms of the attack in the presence of a tumor. For the patients suspected of having pheochromocytomas associated with sustained hypertension, phentolamine (Regitine [5]) and piperoxan (Benodaine [6]) are the drugs of choice for testing, as they lower the blood pressure in the presence of a tumor. No attack is associated with this lowering of the blood pressure. As the blood pressure begins to fall, excessive sweating, when present, is evident over the entire body and not confined to the face and hands.

Various drugs, such as narcotics, sedatives, and the recent blood-pressure-lowering agents, influence the blood pressure during the pharmacologic tests and may give both false positive and false negative results.

Before testing the patient suspected of having a pheochromocytoma with any drug, basal blood pressures should be obtained. This is done by allowing the patient to rest quietly in bed for at least half an hour before the blood pressure is determined. If the resting blood pressure is less than 170 mm. Hg systolic and 110 mm. diastolic, histamine is used for the pharmacologic test, but if the blood pressure is greater than these figures, phentolamine or piperoxan is employed. However, before any drugs are given a cold pressor test is carried out. The rise of the blood pressure during the cold pressor test determines the lability of the blood pressure and may be used as a measuring stick for comparison with the effect produced by the blood-pressure-raising drugs. A lack of rise of the blood pressure during the cold pressor test is an indication that other drugs have been taken within a few hours.

Histamine is administered rapidly intravenously, usually in a dose of 0.05 mg. of histamine base in 0.5 cc. isotonic sodium chloride. The test is considered to be positive for pheochromocytoma if, after a brief drop in blood pressure, the pressure rises at the end of two minutes above that reached in the cold pressor test. The histamine test was employed 20 times on the group of 14 patients with this condition, and the results were positive 19 times and negative only once.[7] Tests with other drugs have given many more false negative results. Phentolamine, one of the most reliable drugs in our experience in testing patients who have sustained hypertension caused by pheochromocytoma, is administered rapidly intravenously in a dose of 5 mg., and the test is considered positive for pheochromocytoma if the systolic blood pressure decreases more than 35 mm. and the diastolic 25 mm. This drug was employed in testing 5 of the 11 patients with sustained hypertension caused by pheochromocytoma, and a positive result was obtained in all cases. If the results of any of the pharmacologic tests appear doubtful or contrary to clinical evidence, the test is repeated and other testing drugs are used. We have had a patient who had

three positive and three negative tests for pheochromocytoma, each test being performed on a different day. Suffice it to say that if a single negative test had been accepted as proof that this patient did not have a pheochromocytoma, the diagnosis would have been missed. No single test can be considered as entirely reliable.

DIAGNOSTIC PROCEDURES TO LOCALIZE TUMOR

Various diagnostic aids have been employed to localize an adrenal tumor if one is suspected. These consist of plain roentgenograms of the abdomen, intravenous urograms, aortograms, perirenal injection of air, and presacral injection of oxygen. It is our practice to utilize routinely only the plain roentgenogram and intravenous

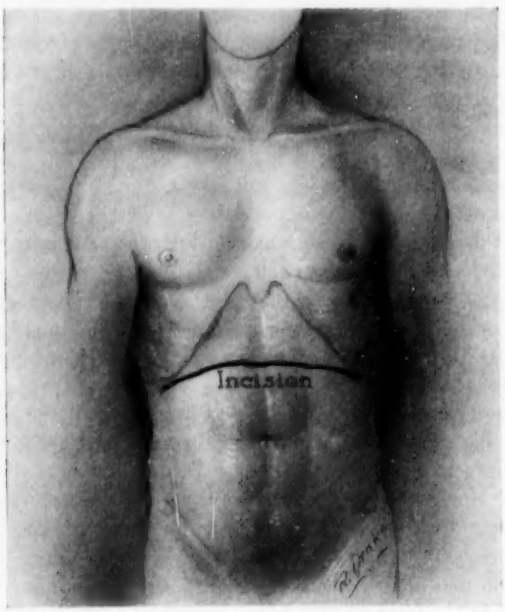

Fig. 1.—Transverse abdominal incision for exposure of adrenal glands and general abdominal exploration for suspected pheochromocytoma.

urogram, as it is not necessary to know prior to operation which gland is involved, and the other procedures are not without some undesirable side-effects or hazards nor are they entirely reliable. They may be employed when considered important in selected cases.

SURGICAL ASPECTS

Fortunately, all patients with pheochromocytoma that we have encountered have been relatively thin. This facilitates surgical exposure of the adrenal glands through an anterior approach. Routinely we employ a transverse incision placed high in the abdomen and curved somewhat upward (Fig. 1). The right adrenal gland may be exposed by retracting the abdominal viscera to the left and downward (Fig. 2). The right kidney is pulled downward also, and the right lobe of the liver is retracted upward. The peritoneum in the region of the upper pole of the kidney is incised, and

the adrenal gland comes into view with a little dissection in this region. The left adrenal gland may be exposed in one of two ways, either by opening the gastrocolic omentum (Fig. 3) or by incising the peritoneum in the region of the upper pole of the left kidney. If the former approach is employed, the gastrocolic omentum is opened relatively widely to the left of the midline. The stomach and tail of the pancreas are then retracted forward and upward. These maneuvers bring the left adrenal gland into view. This is the method of exposure which we prefer. If the other approach is used, the splenic flexure of the colon is retracted medially and downward, and the peritoneum is incised lateral to the bowel. The retroperitoneal space is then entered, the kidney is pulled downward, and the structures overlying the upper pole of the kidney are retracted forward and upward.

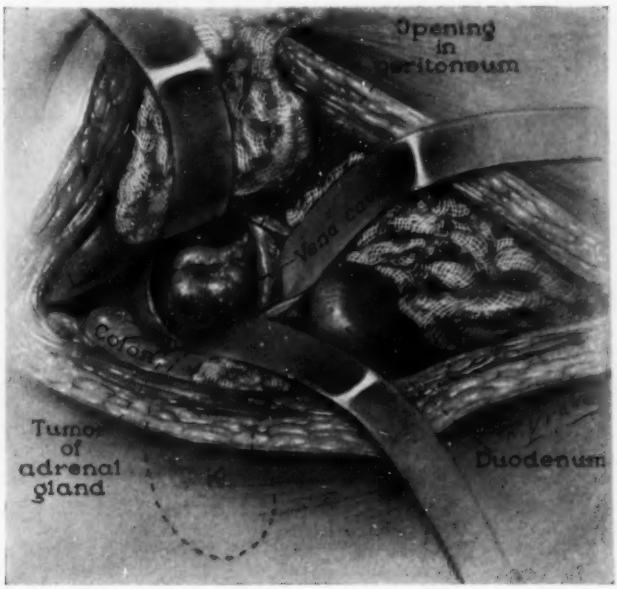

Fig. 2.—Exposure of the right adrenal gland by upward retraction of the liver, medial retraction of duodenum and head of pancreas, and downward retraction of hepatic flexure of the colon and kidney.

It is important for the surgeon who operates for pheochromocytoma to be cognizant of certain pathologic characteristics of these tumors. Thus, although it is true that pheochromocytoma occurs most frequently in an adrenal gland, it may develop wherever chromaffin tissue is present, predominantly along the great vessels in the abdomen or even in the thorax. In one case which has been reported, it occurred in the neck. It is imperative, therefore, if a tumor is not found in the adrenal gland, that careful search be made in other possible sites of origin. An abdominal approach obviously facilitates such exploration. One ectopically located pheochromocytoma was found in the present group of 25 patients.

Pheochromocytoma most frequently occurs as a unilateral single, benign tumor; however, it may be multiple on one side, bilateral, or malignant. The exact incidence of occurrence of each of these unusual findings is difficult to state with certainty.

Multiple tumors are commoner in patients who have sustained hypertension, in contrast with those who have only paroxysmal hypertension. Thus, a total of 18 tumors were removed from 9 of the 11 patients in the former category, and 16 tumors were removed from 14 patients in the latter group. The tumors of two of the patients with sustained hypertension were not removed. The tumor was benign in all cases in which only paroxysmal hypertension occurred, but malignant tumors (with metastasis) were found in 4 of the 11 patients who had sustained hypertension. It is of interest to note that in this series of 25 patients from whom a total of 34 tumors were removed, 23 tumors arose from the right adrenal gland, 9 from the left adrenal gland, and 1 was extra-adrenal in origin. Only one patient had an inoperable tumor.

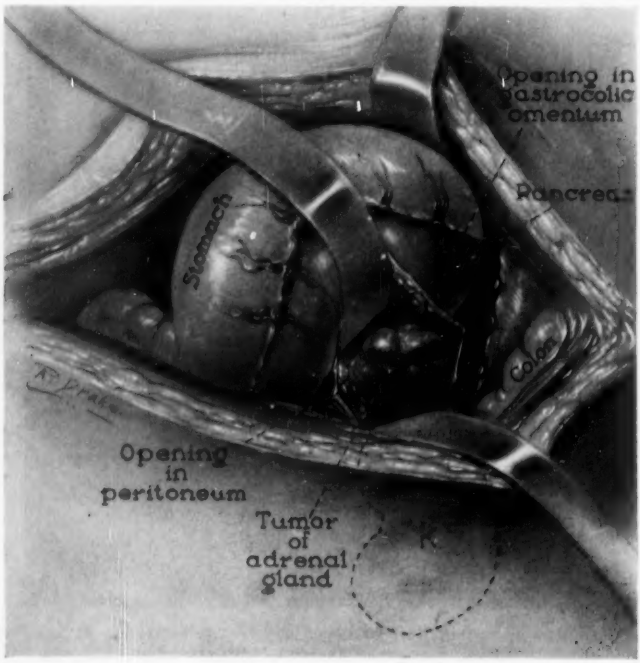

Fig. 3.—Exposure of the left adrenal gland through the gastrocolic omentum with forward and upward retraction of the stomach and tail of the pancreas and downward retraction of the kidney.

The tumors ranged from 10 to 575 gm. in weight; the largest and smallest tumors were found in patients who had only paroxysmal hypertension. We have removed as many as three distinct tumors from the vicinity of one adrenal gland. Characteristically, blood pressure falls precipitously at the time when a pheochromocytoma is removed. If such a fall does not occur, the surgeon should strongly suspect remaining tumor tissue.

During the surgical removal of one of these tumors, the surgeon should palpate and "squeeze" the tumor as little as possible, as such maneuvers may result in the blood pressure reaching alarming heights. Likewise the blood vessels of the tumor should be secured as soon as possible in order to obviate too great pressor effect

during mobilization and extirpation. Fortunately, a pheochromocytoma causes no significant alteration in the important functions of the adrenal cortex. If bilateral tumors are present, it is almost always possible to preserve some adrenal tissue on one or both sides. If this is not possible, immediate and vigorous steps must be taken to combat adrenocortical insufficiency.

OPERATIVE AND POSTOPERATIVE CARE

Extremely close and careful observation of the patient during and after operation for pheochromocytoma is essential. Wide variations in blood pressure may occur during operation, as pressor substances are liberated from the tumor in excessive amounts. Immediately after removal of the tumor, the arterial tension may fall to alarming levels because of the abrupt disappearance of major amounts of these substances from the blood stream. The pronounced hypotension is usually more alarming if the tumor has caused sustained hypertension than if only paroxysmal hypertension has existed preoperatively. It is our practice always to insert a needle into a vein before induction of anesthesia. The blood pressure is recorded by an observer other than the anesthetist at intervals of one minute throughout the operation. Characteristically blood pressure will rise moderately as anesthesia is induced and the incision is made. As the tumor is palpated and manipulated, the systolic blood pressure may rise, if unchecked, to 300 mm. Hg. The depressor drug, phentolamine (Regitine), is used to control these pronounced hypertensive effects; usually 5 mg. is given intravenously. Often 5 mg. of phentolamine is given during induction of anesthesia when the blood pressure rises; this may prevent further elevation. However, if the blood pressure becomes elevated later during the operation, an additional 5 mg. of phentolamine may be given whenever necessary.

After removal of the tumor, supportive measures are necessary usually for the hypotension which follows. At this time infusion of a solution consisting of 4 mg. of levarterenol (Levophed) per liter of isotonic sodium chloride solution is begun. Larger amounts of pressor drugs are required as a rule if the patient has experienced sustained hypertension preoperatively than if only paroxysmal hypertension has occurred.

Postoperatively the patient should be kept under constant observation for a period of at least several days. It has been our experience that the systolic blood pressure if unassisted will fall definitely to less than 100 mm. for one to three days after operation, and the level of hypotension may become alarming. Because of this fact, we employ during this period constant intravenous administration of 4 to 8 mg. of levarterenol in each liter of dextrose, rather than saline solution. Arterial pressure is then controlled in a satisfactory manner by altering the rate of flow of the intravenously administered dextrose which contains this pressor agent. It should be mentioned that too high a concentration of levarterenol administered intravenously over a period of some hours may cause sloughing of the overlying skin.

RESULTS

One or more tumors were removed from 23 of the entire group of 25 patients, and there was no operative mortality. In one patient an inoperable tumor was found, and on one, operation was not performed. All 14 patients with paroxysmal hypertension were relieved of their paroxysmal attacks after operation, and none of those followed adequately have had any recurrence of attacks. One of these patients had

ocular changes of hypertension, Group 2, and blood pressure ranging from 180/120 to 150/104 before the operation. Three years after operation blood pressure on two occasions was 118/80 and 120/90, and the changes in the ocular fundi had reverted to those of hypertension, Group 1. Another patient had funduscopic changes of hypertension, Group 1, with the blood pressure fluctuating between 174/130 and 152/122 before operation. One year after operation blood pressure on one occasion was 142/100.

Of the group of 11 patients who had sustained hypertension, 4 had malignant pheochromocytomas with local invasion or distant metastasis or both. Three of these died, but one is still living. One of the three that died had an inoperable tumor, another was not operated on, and the third had the tumor removed.

The patient with malignant pheochromocytoma who is still living returned to the clinic in 1953. A malignant pheochromocytoma had been removed from the right adrenal in 1950.[8] About a year before his return he had started to have attacks of epigastric distress, perspiration, throbbing headache, weakness, and a tired sensation in the legs. These attacks occurred at least once a day and usually lasted five to seven minutes. Examination revealed blood pressure of 160/120. The basal metabolic rate was +36%; the value of blood sugar was 125 mg. per 100 cc. Two tests with phentolamine and one with piperoxan were positive for pheochromocytoma. The abdomen was explored and tumors were found along the left side of the aorta from the inferior edge of the pancreas to the bifurcation of the aorta. One bilobed tumor was about 4 to 5 cm. long and 2 cm. in diameter, and a smaller one just inferior to this near the bifurcation on the left side of the aorta was about 15 mm. in diameter. These tumors were exceedingly vascular and adherent but were removed. The left adrenal gland was normal to palpation. There was no recurrence in the region of the previously removed tumor of the right adrenal and right kidney, and no tumors were palpable along the right side of the aorta. Postoperative convalescence was uneventful, and on the 12th postoperative day basal metabolic rate was +10% and blood pressure was 150/100. To date the patient has been completely relieved of his attacks.

Of the three patients with sustained hypertension, Group 4, one patient died as a result of metastasis. The hypertension of another reverted to Group 1, six years after operation. The third patient with hypertension, Group 4, reported recently that blood pressure is near normal and that vision is normal; consequently, it is reasonable to assume marked improvement in the retinal picture.

Of the four patients with hypertension, Group 3, one patient has hypertension, Group 2; one has an essentially normal fundus three years later; one had normal blood pressure one year after operation but no funduscopic examination was performed, and one stated that blood pressure is normal.

These results indicate that patients with sustained hypertension of Groups 4 and 3 resulting from benign pheochromocytomas can be expected to be "cured" of their hypertensive disease in that they become free of their symptoms, become normotensive or near-normotensive, and their funduscopic picture reverts to normal or near normal. The two living patients who had hypertensive changes, of Group 1 or 2, are both well.

SUMMARY

Pheochromocytoma may cause either paroxysmal or sustained hypertension. The tumors of 14 of the 25 patients reported on were considered to be functioning paroxysmally because intermittent attacks of hypertension dominated the clinical picture and the blood pressure was normal or only slightly elevated in the interval between the attacks. The tumors of 11 of the patients were considered to be functioning continuously because the hypertension and symptoms were persistent. The

diagnosis of paroxysmal or of sustained hypertension caused by pheochromocytoma may be difficult to establish. In our experience, histamine is the most reliable drug for use in diagnosing pheochromocytoma that causes paroxysmal hypertension, and phentolamine (Regitine) and piperoxan are the most valuable drugs for use in diagnosing pheochromocytoma that causes sustained hypertension.

Pheochromocytomas are usually unilateral, benign, and single and arise usually from an adrenal gland, but exceptions in all these regards do occur. Careful and frequently repeated observations of the blood pressure during operation for pheochromocytoma are essential, and appropriate depressor and pressor drugs should be available for prompt administration during operation. Hypotension commonly follows removal of a pheochromocytoma and requires treatment with pressor agents.

Results following removal of a pheochromocytoma which has caused intermittent hypertension are uniformly good. Likewise, results following removal of a benign tumor which has caused sustained hypertension are good. If the tumor is malignant, recurrence and metastasis may be responsible for death of the patient; results with regard to hypertension, however, are good.

DISCUSSION

DR. FRED R. HARPER, Denver: Last year Dr. Marvin Johnson and I presented the case of a young woman with Cushing's syndrome, in which we first did a bilateral adrenalectomy. The signs and symptoms returned during the next year; consequently, we did a total adrenalectomy on one side and a 95% removal on the other side. This patient had no recurrence of the Cushing's syndrome and required no cortisone until the latter months of a recent pregnancy. This pregnancy has since terminated, with delivery of an apparently normal baby.

DR. ROBERT M. MILES, Memphis: I appreciate so much the privilege of the floor, and wish to congratulate Drs. Priestley and Kvale upon such a comprehensive résumé of the subject of pheochromocytoma.

We should like to mention two cases of pheochromocytoma that bear out the essayists' thesis that serious sequelae frequently recur in pheochromocytoma when they are not recognized and removed. Oddly enough, both these cases were characterized by unexplained gastrointestinal hemorrhages.

The first patient was a 35-year-old white man who had had intermittent attacks of nausea, vomiting, epigastric pain relieved by alkalies, weakness, perspiration, and tarry stools for three years. On several occasions he was almost exsanguinated and many transfusions were necessitated.

Exploratory operations were performed twice by competent surgeons, with no cause for the hemorrhages being found. After several hemorrhages and hospital admissions, hypertension was exhibited with the attacks. Piperoxan (Benzodioxan) tests were positive; the histamine test, negative. This was in the early days of the piperoxan test, and, because of lack of confidence in the test and the two previous negative explorations, the attending physician was reluctant to recommend surgery.

The attacks continued, with intermittent hypertension and massive gastrointestinal hemorrhages, and were treated for a period of about two years, at which time the hypertension was sustained and the internist became convinced of the diagnosis and recommended surgery.

The day before the operation was scheduled the patient developed an extreme degree of hypertension, over 300 mm. Hg systolic, with subarachnoid, cerebral, and subretinal hemorrhages, and he died. Necropsy revealed a large pheochromocytoma of the right adrenal gland but no abnormalities of the gastrointestinal tract.

[Slide] Notice the size of this pheochromocytoma, which has been bisected down the middle. It was about 6 cm. in diameter.

A second patient was more fortunate. He was a 39-year-old white man, who had hematemesis and tarry stools three years prior to admission, with negative x-ray findings. Five months prior to admission, he developed intermittent attacks of weakness, nausea, extreme

pallor of the hands, headaches, and syncope accompanied by transient hypertension of moderate degree. During the hypertensive episodes, phentolamine (Regitine) tests were positive. Histamine tests were positive when he was normotensive.

A pheochromocytoma of the left adrenal gland was removed transabdominally in February, 1953, with cessation of attacks and prompt return of the pressure to normal.

[Slide] Note that this is much smaller, being about 4 cm. in diameter.

It is suggested that gastrointestinal hemorrhage is occasionally a complication of pheochromocytoma, and this possibility should be remembered in hypertensive patients with unexplained gastrointestinal hemorrhage.

DR. JAMES T. PRIESTLEY, Rochester, Minn.: Speaking of diagnostic methods other than the pharmacologic tests, there are a number of procedures which have been employed, such as a plain roentgenogram of the urinary tract, intravenous urogram, perirenal injection of air, presacral injection of oxygen, or an aortogram. Ordinarily, we do not use any of these in routine examinations, except a plain roentgenogram and the intravenous urogram. Perhaps some of these other methods should be employed more extensively.

In certain patients, uncertainty regarding the diagnosis of pheochromocytoma may persist even after evaluation of a carefully taken history and repeated pharmacologic tests, as now performed. In some patients of this type an exploratory operation may be advisable in order to be certain whether such a tumor does or does not exist. Unless this is done the true cause of the patient's symptoms may be overlooked and an opportunity will be lost to cure the hypertension which exists.

I agree that the transthoracic approach does give very fine exposure, as Dr. Sweetser brought out. However, if the tumor is not found in the adrenal glands, one does want to explore the rest of the abdomen, and for that reason we have preferred the abdominal approach, just because it seemed somewhat simpler and easier.

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THIMETHAPHAN CAMPHORSULFONATE (ARFONAD) IN GENERAL SURGERY

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THIMETHAPHAN camphorsulfonate (Arfonad) is the latest in a series of agents and techniques designed to lower blood pressure selectively and thus to reduce bleeding during surgical operations. Attempts to control bleeding are as old as surgery itself. Vasoconstrictor substances, tourniquets, manual compression and temporary occlusion of large vascular trunks, and deep anesthesia are only a few of the methods which have at one time or another been employed. However, only in recent years has it become possible to approach solution of this problem by the deliberate induction of circulatory hypotension, unattended by the feared hazards of a shock-like state. In the last few years, efforts have been concentrated upon improving both controllability and reversibility of such induced hypotension, thus increasing the over-all safety of the method.

INDUCED HYPOTENSION AND SHOCK

Before discussing the various aspects of induced hypotension, it is well to review briefly the physiopathological basis of the more recent methods of induced hypotension and to contrast them with what occurs during oligemic shock.

In response to the sudden loss of circulating blood volume, the body reacts by general metarteriolar vasoconstriction in vast areas not immediately vital to survival and dilatation in some vital areas as well. Thus an attempt is made by the body to adjust the vascular bed to the available circulating volume and to maintain a near-normal hemodynamic system. To the same end, fluid is transferred into the blood stream from the interstitial tissue spaces. The heart rate accelerates in order that the minute volume may be kept as close to normal as possible and an adequate amount of oxygen be supplied to vital tissue per unit of time despite diminished circulating volume. Thus develops the picture of "incipient," or as it is sometimes called, "compensated shock," characterized by a near-normal or even elevated blood pressure with tachycardia and signs of intense cutaneous vasoconstriction, such as pallor,

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From the Department of Surgery (Anesthesiology), University of Illinois College of Medicine, and the Research and Educational Hospitals (Drs. Sadove and Gleave).

beads of perspiration, and retarded capillary refill time. If adequate treatment is not undertaken at this stage, all the compensatory forces just enumerated may not be able to maintain efficient circulation and tissue oxygenation, and vasoconstriction will yield to dilatation of arterioles with secondary capillary dilatation; thus peripheral congestion and stasis develop with consequent diminution of venous return and of cardiac output. This, in turn, leads to hypotension and the advent of fully developed shock. There now will supervene an ever-increasing oxygen want of vital tissues which will eventually affect the capillary wall itself. When this occurs, the vessels will no longer be able to retain their contents, and fluid will leak out of blood vessels, thus further crippling circulation. Damage from tissue hypoxia then reaches such proportions as to make restitution to normal impossible; shock has now become "irreversible."

Induced hypotension by means of spinal anesthesia or drugs which block autonomic ganglia is brought about by a mechanism fundamentally different from the one just described. Here vasoconstrictor impulses are interrupted, leading to initial vasodilatation rather than constriction. Blood pressure falls because of the vastly increased vascular bed thus created and the great reduction of peripheral resistance. Capillary circulation remains adequate and so do venous return and cardiac output. In the presence of adequate oxygen tension in the blood, tissue hypoxia does not ensue and the blood flow to the vital organs is not significantly reduced.[1] It has been shown that permanent damage does not ensue to vital organs as long as their oxygenation is well maintained and excessive degrees of hypotension for prolonged periods of time are avoided.[2] For instance, kidney secretion will cease because of the insufficient head of pressure, but the nephron unit remains intact and urinary secretion will be fully resumed when the blood pressure rises again to allow filtration to take place.[3] Heart, liver,[3] and adrenals remain equally uninjured. Brain damage also should not occur from reasonable degrees of induced hypotension, but adequate blood supply of that organ must be assured by avoidance of undue elevation of the head above the level of the heart.[4] Because of the presence of vasodilatation the skin is dry, warm, and pink, and capillary refill time is always normal; superficial veins are slightly dilated. Indeed, any deviation from this, or the advent of air hunger or similar signs of difficulty must never be tolerated, as they indicate that factors other than the ones just described have supervened and that tissue hypoxia is developing.

GENERAL INDICATIONS OF INDUCED HYPOTENSION

Reduction of bleeding during operations may be a matter of convenience rather than necessity, as, for instance, in many orthopedic procedures where application of a tourniquet will facilitate identification and repair of structures; or reduction of bleeding may be a matter of more or less stringent necessity. In some of the latter circumstances only may the induction of hypotension be indicated; it is never justified for mere convenience. In general, the indications for hypotension may be summarized thus:

1. Control of bleeding when the operation could not be undertaken or would entail an exceptional hazard if more conventional methods were employed.

2. Diminution of trauma because of improved visualization of the field.

3. Inability to replace blood for technical reasons in amounts that would be required if hypotension was not used. This, for instance, may occur in cases of rare blood-group combinations.

4. Control of dangerous hypertension.

5. Treatment of pulmonary edema secondary to hypertension in the pulmonary bed.[5]

6. Facilitation of intracranial exposure because of better visualization and reduction of brain volume.

7. Conservation of time in those cases in which speed is of the essence. The time factor, however, must significantly benefit the patient and must not be an indication if it merely serves the convenience of the surgical team.

INDUCED HYPOTENSION BEFORE ADMINISTRATION OF THIMETHAPHAN CAMPHORSULFONATE

In 1946 Gardner described his method of controlling bleeding during operations by induced hypotension.[6] In this technique arteriotomy is performed, and blood is withdrawn until the blood pressure has fallen to approximately 80 mm. Hg in the normotensive patient. Marked reduction of bleeding can thus be achieved, and any further fall of pressure is countered by the fractional arterial reinfusion of the previously withdrawn and suitably preserved blood. At the end of the operative procedure the remaining blood is reinfused, together with such additional amounts of bank blood as circumstances and the patient's condition may demand. Obviously this method of producing hypotension is one of inducing a state of preshock in that it utilizes the same physiopathological mechanisms as are concerned in the establishment of hemorrhagic shock. The margin of safety, therefore, between this state of preshock and the development of frank shock is relatively narrow; like shock, it is based upon a mechanism of metarteriolar constriction with consequent potential tissue hypoxia, and therein lie the principal hazards of this technique of induced hypotension.

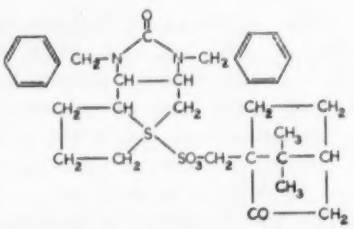
In 1948 Griffith and Gillies [7] opened a new chapter in induced hypotension when they described their method of "total," or, as it is now more aptly called, "hypotensive," spinal anesthesia.[8] In this technique primary metarteriolar dilatation is produced by the preganglionic paralysis of the vasoconstrictor impulses mediated through the sympathetic nervous system. Vasomotor control being abolished to a large extent, blood will tend to gravitate to dependent parts of the body; thus elevation of the legs above the level of the heart will provide an almost bloodless field in the lower extremities; with the patient in the lateral position and the kidney rest elevated, much blood loss can be averted in the removal of a hypernephroma or during a splanchnicectomy; with the patient in the Trendelenberg position, marked diminution of blood loss can be achieved during the operation of pelvic exenteration. In operations about the head and neck, the situation is more complicated. Elevation of the head will also provide the surgeon with a near bloodless field, but at the same time it may jeopardize adequate oxygenation of the brain itself.[4] It is significant that almost all cerebral complications from this method have been reported from abroad, where elevation of the head during head and neck surgery under hypotension is being widely practiced. We believe that the potential danger of cerebral involvement is too high a price to pay for a bloodless field.

The method of hypotensive spinal anesthesia, while satisfactory in the hands of a few who have gained wide experience with it, has not achieved widespread acceptance in this country. Hypotension tends to be fixed, and, consequently, blood-pressure levels cannot be easily adjusted from moment to moment to the varying surgical needs. The technique is somewhat complicated and time-consuming and combines

the hazards of spinal anesthesia with those of general anesthesia with which it is commonly supplemented. Attempts have therefore been made to achieve metarteriolar dilatation by the use of autonomic blocking drugs; of these, the methonium compounds and thimethaphan camphorsulfonate have been the ones most widely accepted. Hexamethonium and pentamethonium have been the earlier of these agents,[9] but their use is accompanied by a number of disadvantages. Foremost of these are their relative uncontrollability and unpredictability of response. It is not possible by the use of these agents to predict or to control adequately the degree of hypotension which will accompany the injection of a certain dose. Vasopressors may be needed to reverse undue depth or duration of hypotension, and if, thereafter, further hypotension becomes desirable, it cannot be obtained as long as the vasopressor drug remains active. The methonium compounds exhibit marked tachyphylaxis, that is, diminished response to subsequent doses. Furthermore, the fall of blood pressure may be abrupt and excessive, or no response may be observed at times even after the administration of very large amounts of these agents. Drugs so unpredictable and uncontrollable have obvious serious disadvantages in clinical practice, and any agent which can be more easily controlled represents a marked advance. Such an agent, we believe, is thimethaphan camphorsulfonate.

THIMETHAPHAN CAMPHORSULFONATE

Pharmacology.—Thimethaphan camphorsulfonate is a thiophanium derivative with the following chemical name: *d*-3,4(1′,3′-dibenzyl-2′-keto-imidazolido)-1, 2-trimethylenethiophanium *d*-camphor sulfonate. Its structural formula is as follows:



Structural formula of thimethaphan camphorsulfonate.

Many aspects of the pharmacology of thimethaphan camphorsulfonate in man still lack clarification, but it may be said that hypotension is due at least in part to metarteriolar dilatation caused by ganglionic blockade. It is possible that histamine release also may enter the picture, but although proved in dogs, this has as yet not been demonstrated in man.[10] Thimethaphan camphorsulfonate is an ultra-short-acting agent: Its effect is so evanescent that the agent must be administered in a continuous intravenous infusion if vasodepression is to be maintained. Thus the level of blood pressure may be adjusted from moment to moment, depending on the surgical need of the moment. Thimethaphan camphorsulfonate is markedly facilitated by general anesthesia and by drugs with a vasodepressor action, such as morphine and meperidine (Demerol). The deeper the plane of anesthesia the more marked the response to like doses. Similar to the methonium compounds, thimethaphan camphorsulfonate is also potentiated by the administration of procaine hydro-

chloride or procaine amide. This is important in the infrequent cases which show some degree of refractoriness to thimethaphan camphorsulfonate. In the vast majority of cases, minute-to-minute control of blood pressure is easily obtained by simply adjusting the rate of flow of the intravenous infusion. Nothing is definitely known regarding the elimination of thimethaphan camphorsulfonate. However, the rapidity with which its effect disappears clinically would lead one to postulate that it is inactivated in the body with considerable speed.

Observations carried out by us on human volunteers support the clinical observation of the importance of adequate surgical anesthesia when thimethaphan camphorsulfonate is used to induce hypotension. In conscious patients with a normal blood pressure the degree of vasodepression is self-limited to a final systolic pressure of approximately 90 mm. Hg, even with doses up to five times those usually used in clinical practice. A plateau is maintained at this level unless changes in position are assumed or general anesthesia is superimposed. No attempt has been made to break through this plateau, if this should be possible, by further increasing the amount of thimethaphan camphorsulfonate administered. From our observations, it would therefore appear that even in the presence of ganglionic blockade other compensatory mechanisms remain intact which can be subdued only by general anesthesia. In those volunteers the following additional observations were made: Responses to hypoxia and hypercarbia remain unimpaired. No essential changes could be demonstrated in venous pressure, electrocardiograms, and electroencephalograms. Plethysmography reveals an increase in peripheral pulse volume. The stroke volume of the heart is reduced by 5 to 10 cc., but the minute volume is not markedly changed. Changes in position of the patient will cause a redistribution of blood to the dependent parts of the body.

GENERAL CONSIDERATIONS

To date we have had more than 200 cases in which thimethaphan camphorsulfonate has been used as the "hypotensive agent" during anesthesia, and on the basis of our results and observations we have arrived at these following conclusions as to its use in clinical surgery:

Induced hypotension by ganglionic blockade, abolishing as it does normal vasomotor control, requires that a normal circulating blood volume and normal oxygen-carrying capacity be present at all times in order that tissue oxygenation may be maintained at an optimum level. Hence, blood loss, unless minimal, must be replaced *pari passu* with any loss that might be occurring. Hypotension must never be induced after severe blood loss has occurred in order to avert further bleeding. Rather, the operation should, if possible, be terminated and may then be completed at a second stage after the circulatory *status quo* has been reestablished. While the operation under hypotension is in progress, especially close attention must be paid continuously to early signs of peripheral vascular failure, indicated by any of the following signs: tachycardia, air hunger, perspiration, pallor, venous constriction, or increased capillary refill time. The patient's skin must at all times remain pink, dry, and warm, with the pulse rate only slightly above normal levels and breathing regular and easy. Superficial veins are usually moderately dilated. The acute head-up position is never adopted; in rare instances the head has been elevated 2 to 4 in. (5 to 10 cm.) above the horizontal plane of the body. By maintaining the operating table on a level, we have been able to obviate the dangers of cerebral ischemia: A bloodless field is, of course, thus never obtained in operations around the head and

neck, but control of bleeding points is greatly facilitated and blood vessels continue to retract. Bleeding is reduced to such an extent that it has been possible to remove large meningiomata with comparative ease in patients in whom the operation had previously been abandoned because of uncontrollable bleeding.

The blood pressure is lowered and then raised again gently and gradually by increasing or decreasing the rate of infusion of thimethaphan camphorsulfonate; the pressure is at all times kept at the highest level compatible with the surgical procedure at hand at any particular moment. Hence this method of induced hypotension may truly be termed "controlled hypotension," in contradistinction to all other methods or drugs hitherto available. If return of normal pressure is desired at a rate faster than occurs when the administration of this evanescent agent has been discontinued, a very small quantity of any of the common vasopressors will bring about the desired results.

INDICATIONS AND CONTRAINDICATIONS

The early enthusiasm for hypotension in anesthesia has now given ground to a more sober attitude and more stringent assessment of indications. We do not believe this method to be indicated in operations associated with mere marked, but not excessive, blood loss if adequate facilities for replacement therapy are available. We advocate the technique in the following types of cases:

1. Neurosurgery
   Brain tumors; cerebrovascular aneurysms; operations in areas where even slight bleeding markedly interferes with visualization and with the surgeon's work; and cases of difficult exposure, because hypotension causes some shrinking of the brain and renders it more compressible.
2. Peripheral vascular surgery
   Anastomosis of large blood vessels is greatly facilitated by hypotension. The method is useful in aortic grafts and transplants, coarctation operations, and operations for arteriovenous fistula.
3. Removal of highly vascular neoplasms: e. g., hypernephroma
4. Operations associated with great blood loss: evisceration procedures, pancreatectomy, splenorenal shunts
5. Patients with unusual blood-group combinations for whom adequate amounts of blood cannot be obtained
6. Control of dangerous systemic hypertension and treatment of pulmonary edema due to pulmonary hypertension

Contraindications, as always, are relative, and allowances may have to be made in exceptional circumstances. The following conditions, in our opinion, constitute such contraindications:

1. Shock, both incipient and frank
2. Inadequate availability of fluids
3. Inability to replace blood for technical reasons
4. Inadequate skill on the part of the anesthesiologist
5. Severe visceral disease, especially of liver and kidneys
6. Degenerative disease of central nervous system
7. Severe cardiac disease
8. Hypovolemia
9. Uncorrected anemia
10. Arteriosclerosis

SUMMARY

A new method of inducing true "controlled hypotension" has been presented. This method is characterized by minute-to-minute control of the level of blood pressure desired. The indications and contraindications of this new method have been enumerated in detail, and emphasis is placed on the relatively few indications of controlled hypotension in general surgery. We believe that when it is indicated, thimethaphan camphorsulfonate (Arfonad) represents a valuble aid to surgery.

DISCUSSION

DR. F. H. BENTLEY, Portland, Ore.: In my old department of surgery, at Newcastle-upon-Tyne, England, we did not have much experience with this method, because there we were still predominantly cautious, and Dr. Pask, professor of anesthesiology was not at all certain he wished to use the method extensively, it being his view—rather like the speaker's—that it was as yet a research method.

I went up to Edinburgh a number of times to watch the work being done by Dr. Gillies in Sir James Learmonth's department. One could not help but be profoundly impressed by the facility given to the surgery, particularly of the neurosurgical type. For instance, I have seen bilateral lumbar sympathectomy done in 50 minutes, complete from start to finish, with no bleeding and with smooth recovery of the patient.

When this method is employed by men skilled in its use, the incidence of postoperative troubles seem to be very small. And yet, many of us still cling to a preference for that form of surgery and anesthesia which shows the blood pressure record as a straight line throughout the operation! Whether that means we are a reactionary rear guard fighting a losing action against progress, or whether it is just plain common sense, I am really not able to judge at the present time.

DR. DAVID L. REEVES, Santa Barbara, Calif.: This obviously has been such an important feature in neurological surgery that it has caused a great deal of consideration and a lot of mixed opinions during the last four or five years.

This was originally brought in, of course, by the so-called total spinal anesthesia which reduced the pressure usually lower than Dr. Sadove has mentioned and, unfortunately, was not as easily controlled. True enough, the surgery of difficult vascular meningiomas and also the surgery of aneurysms was tremendously facilitated, but because of the thrombosis which followed, it has been rather generally abandoned, as the so-called total spinal anesthesia.

The hexamethonium types of drugs were then employed, and they have been useful in bringing pressure down to 80 or 60 and have been used with some enthusiasm, but at the present time that enthusiasm has been greatly tempered, and the drug is not used as frequently as it was a few years ago. It has a definite place in certain types of intracranial surgery. It may very well be that trimethaphan camphorsulfonate (Arfonad) will give us better results than the previously used hexamethonium types of drugs.

I think it will be interesting to see what the complications may be within the next few years, but in all events, I can assure you the initial enthusiasm has been seriously tempered. Nonetheless, it offers a definite adjunct for neurological surgery, which cannot be denied, and which, in certain cases, is almost indispensable.

DR. MAX S. SADOVE, Chicago: I would like to question our conventional connotation of what blood pressure really means. I am not disagreeing with the previous speaker, but I have seen many patients in shock with a blood pressure of 130, and I have seen many relatively well patients with a blood pressure of 70.

I think the blood pressure means no more than a red cell count. True, it gives us a relative idea as to where the patient is, but it really does not tell much. The important thing to an organ is how much blood is bringing how much oxygen per unit time. The blood pressure is merely a measurement of the internal pressure against the wall of the artery that one happens to be measuring. It does not indicate the total flow through a particular structure at a definite time.

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USE OF CORTISONE IN THROMBOCYTOPENIC PURPURA

Preoperative and Postoperative Management of Patients

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J. RALPH CALDER, M.D.
DETROIT

OF THE many noted physiological effects of adrenocorticotropin (ACTH) and cortisone, perhaps their ability to produce variable degrees of remission in thrombocytopenic states may prove to be one of the most practicable. While splenectomy has been widely used in the treatment of idiopathic thrombocytopenic purpura for over 35 years, the results have not been entirely satisfactory. Welch and Dameshek [1] reported that in a series of 92 patients splenectomized for idiopathic thrombocytopenic purpura, 61% showed complete and sustained therapeutic response and an additional 19% showed a partial response with a great reduction in the bleeding tendency. Most of the mortality associated with splenectomy for this condition has occurred in those instances when it became necessary to operate during an acute fulminating crisis. It is in these hazardous cases that sufficient search may not be made for accessory spleens and also where the splenic capsule may be torn and thus small particles of the pulp transplanted throughout the abdominal cavity. The use of cortisone preoperatively and postoperatively in these critical patients may materially decrease the mortality and morbidity, and it has not, in our experience, caused any untoward effects. The use of cortisone preoperatively in these patients may be considered as being somewhat analagous to the use of antithyroid drugs in the preparation of toxic patients for thyroid surgery.

PATHOGENESIS

The role of the spleen in idiopathic thrombocytopenic purpura is still not completely understood. The most recent studies have postulated the existence of a humoral substance, probably an antibody in the plasma.* Evans and his co-workers [4] have pointed out the resemblances of idiopathic thrombocytopenic purpura to acquired hemolytic anemia, in which "autoantibodies" active on red cells can usually be detected. He demonstrated a platelet agglutinating factor in the serum of some patients with idiothrombocytopenic purpura. Harrington and his associates [2] showed

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* References 2 and 3.

that a transfusion of blood or plasma from most patients with idiopathic thrombocytopenic purpura into normal subjects promptly decreased the platelet counts of the recipients, and that this effect persisted for from five to seven days. It is likely that there may be several varieties of idiopathic thrombocytopenic purpura, since at times there seems to be an increased rate of destruction of platelets and at other times a decreased rate of production seems to be the fault.

Increased capillary fragility, usually always present in thrombocytopenic purpura, is also poorly understood. The vascular defect is improved immediately after splenectomy, while the platelet count increases rather gradually. Capillary fragility and the degree of thrombocytopenia do not necessarily parallel each other, as either may predominate in a given patient.

Although the spleen may eventually be assigned a secondary role in the pathogenesis of thrombocytopenic purpura, splenectomy results in cure of this condition in the great majority of patients.

The various types of thrombocytopenic purpura are shown in the classification given in Table 1.

TABLE 1.—*Classification of Types of Thrombocytopenic Purpura*

Hypersplenism
Idiopathic (platelet autoantibodies)
Symptomatic (associated Hodgkin's disease, Banti's disease, etc.)
Marrow destruction or depression
Irradiation
Drugs
Infections
Tumor replacement

DIAGNOSIS

Examination of the bone marrow is indispensable in the differential diagnosis of thrombocytopenic purpura. Its greatest value may be in diagnosing "secondary" or symptomatic thrombocytopenia and thus averting splenectomy in cases of leukemia and aplastic anemia. The number of megakaryocytes may be normal or increased, but there is a lack of platelet formation; however, this picture may also occur in some toxic and infectious states. Schwartz [5] found increased numbers of eosinophiles in the bone marrow of some patients with thrombocytopenic purpura and thought that these patients had better prognosis both as to possibility of a spontaneous remission and as to benefits from splenectomy. However, neither the eosinophilia of the bone marrow nor the response to cortisone is a good indication of the results which may be obtained from splenectomy. While, in general, a low megakaryocyte count in the bone marrow is a contraindication to splenectomy, a complete evaluation of the total picture by a competent hematologist is required before a decision on treatment may be reached.

The usual diagnostic criteria include (1) increased capillary fragility; (2) increased bleeding time; (3) normal clotting time but poor clot retraction; (4) spleen not palpable or barely so; (5) platelets low in circulating blood; (6) megakaryocytes present in bone marrow in normal or increased numbers, and (7) lack of platelet formation from the megakaryocytes.

EFFECTS OF CORTICOTROPIN AND CORTISONE

Probably the most important effect of adrenocortical activity is the improvement in capillary fragility in thrombocytopenia, regardless of its etiology. Robson [8] showed that capillary fragility was regularly improved, while the platelet count rose irregularly several days after treatment with cortisone. With the demonstration of autoantibodies as an important feature of thrombocytopenic purpura, it has been postulated the role of cortisone is as an inhibitor of the formation of these antibodies.

TABLE 2.—*Treatment of Idiopathic Thrombocytopenic Purpura (1950-1953)*

	Patients, No.
Splenectomy	7
Cortisone and splenectomy	10
Corticotropin and splenectomy	3
Corticotropin or cortisone	12

TABLE 3.—*Distribution of Ages in Twenty-One Cases with Operation*

Yr.	Cases, No.	
1-10	4	(Cases 3, 4, 6, and 10)
11-20	1	(Case 19)
21-30	2	(Cases 22 and 27)
31-40	7	(Cases 31, 32, 33, 35, 37, 38, and 40)
41-50	3	(Cases 47, 47, and 49)
51-60	4	(Cases 51, 53, 53, and 57)

TABLE 4.—*Preoperative and Postoperative Use of Cortisone*

Platelet Counts	Average
Admission	16,500
Preoperative	175,300
Postoperative	441,100

TABLE 5.—*Cortisone Dosage in Cases of Thrombocytopenic Purpura*

	Daily, Mg.	Average, Days
Preoperatively	200-300	10
Postoperatively	50-300	3

The platelet responses to cortisone does not truly prognosticate the response which may be expected from splenectomy, for several cases giving poor results with the use of cortisone have been cured by removal of the spleen.

METHODS AND RESULTS

During the period taken for this study (1950 to 1953), patients with idiopathic thrombocytopenic purpura were treated as shown in Table 2. Splenectomy with corticotropin or cortisone was used in 13 instances, while splenectomy alone was performed upon 7 patients. In this latter group, a decision to do splenectomy had been arrived at after a careful study of the patients, and, as there was no crisis and

the patient's condition was good, it was felt that there was no need for administering cortisone. The 12 patients who have received only cortisone or corticotropin are children or adults who have refused splenectomy. These are being followed closely, as some of them may relapse and require splenectomy.

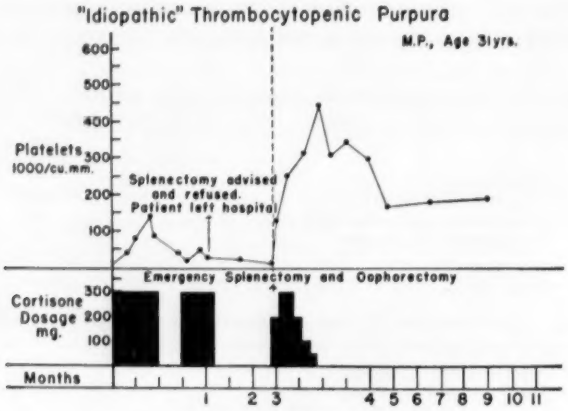

Chart 1.

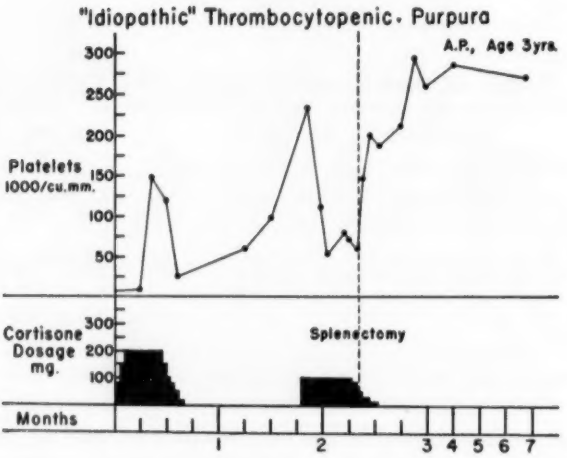

Chart 2.

Of the 25 patients with idiopathic thrombocytopenic purpura who have received cortisone or corticotropin, 11 have failed to respond or have relapsed. At the present time, adults with idiopathic thrombocytopenic purpura are routinely advised to have a splenectomy, and corticotropin and cortisone are not used as a means of treatment but rather for preoperative preparation. The ages of the 21 patients who underwent splenectomy are shown in Table 3. There was no mortality and no morbidity.

In children in whom idiopathic thrombocytopenic purpura is frequently associated with some type of infection a trial of conservative therapy with corticotropin or cortisone is tried under careful observation. When a relapse occurs, splenectomy is advised. As a means of inducing a permanent remission, corticotropin and cortisone therapy has been disappointing.

The platelet response to cortisone is shown in Table 4. It will be noted that these patients were operated upon, with a very satisfactory platelet count. The average preoperative and postoperative management with cortisone is shown in Table 5.

An accessory spleen was found in 2 of the 21 patients who underwent splenectomy. One patient, aged 31 years, had a remission on two occasions following the use of cortisone, but she refused splenectomy. She was admitted in critical condition six weeks later with profuse bleeding from an ovarian cyst, at which time her platelet count was 28,000. Cortisone was administered and an immediate oophorectomy and

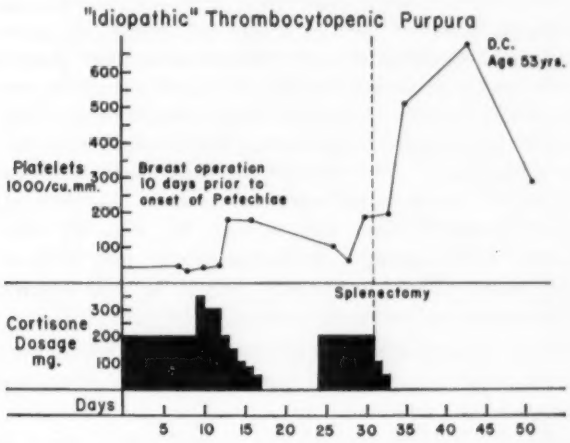

Chart 3.

splenectomy performed with excellent results (Chart 1). An instance of relapses following cortisone therapy with a good result following splenectomy is shown in Chart 2. An instance of thrombocytopenic purpura appearing 10 days after previous surgery is shown in Chart 3. No medicines could be incriminated as an etiological agent, and the marrow studies showed a normal megakaryocyte count. A splenectomy cured her after two courses of cortisone had failed to maintain a satisfactory remission.

COMMENT

Recent reports of splenectomy for idiopathic thrombocytopenic purpura show a very low operative mortality. Zollinger, Martin, and Williams,[6] in 1952, reported 1 death in 57 patients. Lahey and Norcross [7] reported 17; Robson,[8] 19, and Cole, Walter, and Limarzi,[9] 26 splenectomies for this condition without a death. Coller, Blain, and Andrews [10] also reported a very low mortality for splenectomy before cortisone was used. Since, prior to this study, one of us (B. E. B.) performed splenectomy upon 15 patients with idiopathic thrombocytopenic purpura without

mortality, it cannot be said that the use of cortisone has lowered the mortality. When the bleeding tendency is present, it is prudent to administer cortisone in order that surgery may be performed under more favorable conditions.

It is obvious that if satisfactory results are to be obtained a careful study of every aspect of the patient with thrombocytopenia must be made. If an infection is present or if drugs or allergens are implicated, conservative management is indicated. When bone marrow replacement is found, the primary condition responsible for this must be treated. When acute thrombocytopenic purpura is superimposed upon a chronic condition, such as congestive splenomegaly, Hodgkin's disease, etc., the correction of the purpuric element may give the patient several additional years of life.

The majority of children show a tendency toward a spontaneous recovery, and, consequently, conservative measures with hormonal therapy are indicated as a trial at least. In adults there is less tendency to a remission and of course the much greater hazard of cerebral vascular accidents. One of our patients who had refused operation on several occasions died of a cerebral accident in spite of cortisone therapy. The generalized effects of continued cortisone therapy are multiple and so varied that its use for prolonged therapy of thrombocytopenic purpura may be very dangerous and inadvisable. In most instances these hormones have their greatest usefulness in the management of fulminating hemorrhage and in the preoperative preparation for splenectomy.[11] The operative mortality may be decreased as a result of this preparation with cortisone, and when the operation is performed under better conditions, a more complete search may be made for accessory spleens. When a spleen is removed rapidly during a crisis, the capsule may be torn and splenic transplants may result. This complication should be lessened when adequate preparation with cortisone precedes the surgery.

The response to corticotropin and cortisone is similar when comparable doses are used. The fact that cortisone has a more direct action would appear to make it preferable for use in this condition.

Wound healing appeared to proceed at a normal rate in every instance. No wound weakness, separation, or postoperative hernia occurred.

SUMMARY AND CONCLUSIONS

Twenty-one patients with idiopathic thrombocytopenic purpura who had splenectomy without mortality are presented. Cortisone was of value in the management of those in the acute phases of the disease.

While corticotropin and cortisone have been disappointing as a form of treatment for patients with idiopathic thrombocytopenic purpura, they are of value in the preparation of patients for splenectomy.

No ill effects from this use of cortisone could be noted, and no postoperative complications occurred.

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EVALUATION OF SURGICAL TREATMENT FOR DISTURBANCES OF THE THYROID GLAND

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MINNEAPOLIS

DURING the past 30 years, many changes have occurred in the character and treatment of the disturbances of the thyroid gland. The changes in the treatment have been concerned mainly in the management of the patient with hyperthyroidism. However, it is a strange paradox that during the development of the antithyroid drugs the number of cases as well as the severity of the toxic goiter has gradually subsided. Now that we have the valuable antithyroid drugs, we rarely see the severely hyperthyroid patient. In fact, in our experience, the hyperthyroidism we have encountered has been so relatively mild that we have found a decreasing need for the thiourates. In our series of 1,473 cases, 861 patients, some of whom were adolescents, had variable degrees of hyperthyrodism in the form of true Graves's disease, exophthalmic goiter, and nodular goiter. Of the 861 patients, 21 were children under 16 years of age, the youngest, a child of 8 years with exophthalmos.

The clinical literature reveals that other surgeons are having similar experiences. E. S. Judd, Jr., in discussing the role of the surgeon in thyrotoxicosis, asserts that "propyl thiouracil will have a definite small place as a preoperative agent." He further evaluates this agent by stating that "in those few cases of thyrotoxicosis in which the hyperthyroidism cannot be brought under proper control for surgical treatment by the use of Lugol's solution alone, propyl thiouracil is administered." Curtis stated that "the risk of the drug superimposed on the risk of the disease exceeds the mortality rate with treatment of iodine and competent surgery." Curtis further states:

> It is our opinion that the now well established preoperative management of the patient with hyperthyroidism followed by competent surgery will remain the treatment of choice until an antithyroid drug, which will have a risk less than that of the disease, is synthesized. Surgery then remains the treatment of choice in the management of the great majority of patients with hyperthyroidism.

Lahey states that patients with very mild hyperthyroidism are still prepared with strong iodine solution (Lugol's solution) alone. He feels that antithyroid drugs do have a capacity to produce prolonged remissions of mild hyperthyroidism, as does iodine at times, but little hope is held for a permanent remission in patients with severe primary hyperthyroidism with a large gland. He concludes that since the

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mortality of thyroidectomy is now almost nil, surgical removal after the proper preoperative treatment seems to be the proper choice for hyperthyroidism. It is evident then that surgery always has been, and still is, the treatment of choice in the management of the majority of patients with goiter, including those with hyperthyroidism who have been properly prepared.

From the beginning of thyroid surgery, the fear of hemorrhage has been uppermost in the mind of the surgeon. Halsted in his "Operative Story of Goiter" stated "this conspicuous tumor of the neck was a perpetual challenge to the physician and a stigma as well to the surgeon." Because of the generous blood supply of the thyroid, which has been stated to be 100 times as great as that of the brain and 20 times more abundant than that of the kidney, the control of bleeding is still the most important technical problem of thyroidectomy. With this responsibility, the surgeon should be prepared to perform a rapid and clean operation with a technique based fundamentally on the anatomy involved.

It has been observed that many operators will follow no premediated plan of attack, merely excising goitrous tissue and accomplishing hemostasis as removal of the gland progresses. The operative field is soon filled with hemostats, with resulting extra hazard of damage to the recurrent laryngeal nerves. These hemostats, in turn, are replaced with numerous ligatures which delay healing and increase drainage, with a resultant unsightly scar.

It is reasonable to believe that a planned method of procedure with the preliminary application of ligatures to the main vessels supplying the gland will prevent hemorrhage and thereby avert the most serious complication of thyroidectomy, namely, injury to the recurrent laryngeal nerves and damage to the parathyroid bodies. A planned method will also be helpful in obtaining a good functional result, averting recurrence and preventing persistence of hyperthyroidism.

A brief reference to the technique with three illustrations will best emphasize the value of a planned procedure. The incision of the thyroid should be relatively straight. In patients with ordinary-sized goiters, it should be placed about 1 fingerbreadth above the upper border of the sternal ends of the clavicles. In patients with large goiters, because of the resulting looseness of the skin, the incision should be relatively higher to prevent "dropping" of the scar onto the upper chest. The incision should go down to and through the superficial layer of the deep cervical fascia, thereby including the anterior jugular veins which are dissected back with the anterior flap. After the bleeding in the upper flap has been controlled, the lower margin of the wound is undermined for a distance of about 2 cm. This important procedure prevents an "overhanging" of the skin of the upper flap after the wound has healed. Inclusion of the superficial layer of the deep cervical fascia in the flap has the advantage of preventing ecchymosis of the skin in the thin patient. When the prethyroid muscles have been thus exposed without their fascial investments, they can readily be retracted without cutting.

Transverse section, posterior and lateral views of the thyroid demonstrated by our dissections, reveals the advantage of a planned preliminary hemostasis to avert complications in thyroidectomy (Figs. 1 and 2). The close relation of the superior laryngeal nerve to the superior thyroid artery, the course of the recurrent laryngeal nerves as related to the inferior thyroid arteries, and the usual location of the parathyroid glands are clearly shown. It is obvious that a ligature applied to the trunk of the inferior thyroid artery as it emerges from under the carotid sheath will produce

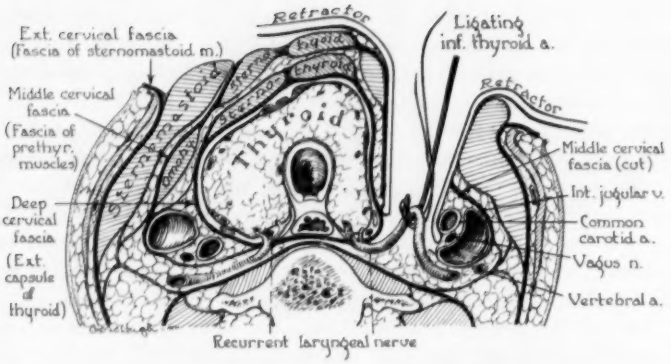

Fig. 1.—Transverse section of neck at level of sixth cervical vertebra, showing preliminary extrafascial approach to inferior thyroid artery. (Reproduced by permission of *Surgery, Gynecology and Obstetrics.*)

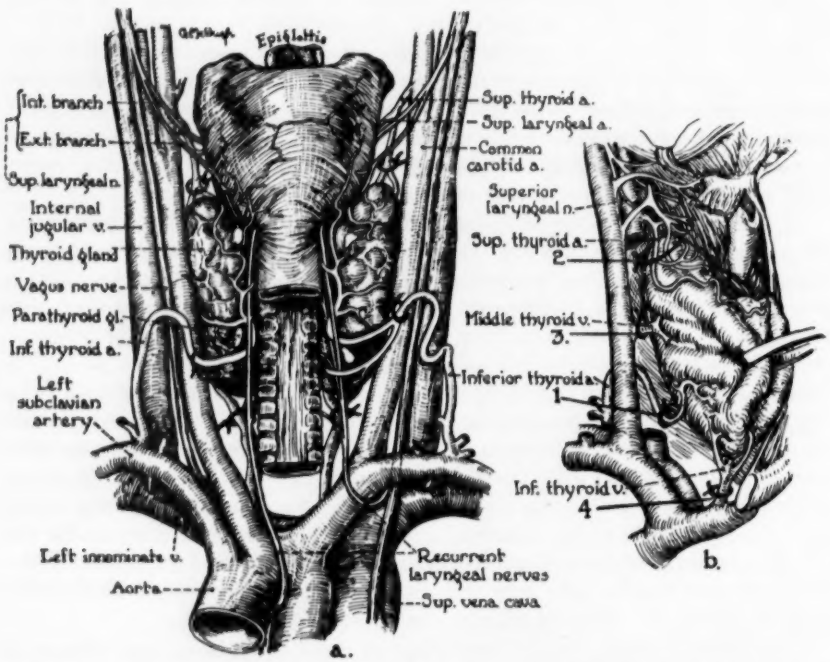

Fig. 2.—Preliminary hemostasis: Ligatures have been applied to (*1*) the inferior thyroid arteries (extrafascially), (*2*) the median thyroid veins, (*3*) the superior thyroid arteries and veins, and (*4*) the inferior thyroid veins. The gland can now be resected deliberately with very little bleeding. (Reproduced by permission of *Surgery, Gynecology and Obstetrics.*)

complete hemostasis. Attempts to apply forceps to its many branches result in less hemostasis and more possible damage to the recurrent nerve. This nerve enters the larynx at the junction of the cricoid and thyroid cartilage. Attention must be called to the danger of injury to the nerve at this point when ligatures are applied to the posterior branch of the superior thyroid artery. Arterial rather than polar ligation will avert this complication. We feel that an attempt to identify the recurrent laryngeal nerve in all thyroidectomies is unnecessary and that such a procedure would often result in injury to the nerve in the attempt to find it. We do feel that identification of the recurrent nerve is important in the very small glands and in the attempt to remove recurrent thyroid tissue. In the latter, the nerve often is displaced from its natural position by scar tissue.

Intralaryngeal examination to note the position of the vocal cords should be a routine preoperative procedure. E. S. Judd, Sr. pointed out years ago that about 5% of the patients coming to thyroidectomy have a previously disabled cord. The large goiter, substernal, intrathoracic, and especially the recurrent goiter are more commonly so affected.

The question has often been raised concerning the blood supply of the parathyroid bodies when all four of the thyroid arteries have been ligated. In 1929 we performed careful dissection of the neck in 31 cadavers to determine the relations of the recurrent laryngeal nerves to the thyroid arteries and further dissected 19 larynges to determine the enervation of the intralaryngeal and extralaryngeal muscles. The study included a careful evaluation of the blood supply of the thyroid and parathyroid bodies. Since that time, we have applied ligatures to the four thyroid arteries preliminary to thyroidectomy in 1,473 patients and proved that no damage was done to the parathyroid bodies. The generous collateral circulation established between the internal laryngeal, internal mammary, and transtracheal vessels, together with the preservation of the posterior capsule over the trachea, leaves an adequate blood supply to the parathyroids.

Recurrent goiter and persistence of hyperthyroidism in the exophthalmic goiter is often due to an inadequate operation. Experience has shown that there is no criterion to determine the exact amount of tissue to remove or the amount that should be left behind. We have found that neglect in the thorough removal of the pyramidal lobe and the inadequate removal of the tissue in the region of the superior poles most frequently accounts for the compensatory hypertrophy and the recurrent hyperplasia of these residual portions of unresected tissue, especially in the toxic cases. Careful inspection for and the removal of small adenomata from in front of the capsule in the lower portion of the lobe by sharp dissection, or better with the ring forceps, prevents recurrence in the adenomatous types of goiter.

Since most thyroid carcinoma occurs in nodular goiter, 6.6% in our series, and in view of the relatively small risk of the operative removal of this type of goiter, we feel that it is advisable to recommend the surgical excision of all nodular goiters unless strong contraindications exist. Hinton and Lord found the incidence of carcinoma to be 7.6% in the clinically benign nodular goiters, as compared with an incidence of 6.7% of carcinoma in the clinically benign breast lesions. We have observed that clinicians have too often used the basal metabolic rate (so important in Graves's disease) as a criterion in determining the need of surgery in all types of goiters. Nodular goiters, which are usually unsightly and frequently cause pressure symptoms, often become malignant and should be removed for these reasons,

in spite of a normal basal metabolic rate. The symptoms of carcinoma as described in textbooks and in the literature are the same as those of far-advanced malignant growths. When these symptoms are present, such as pain, recent rapid growth, a metallic voice, adherence to the surrounding tissues, and invasion of adjacent vessels (which means the penetration of the capsule), it is usually too late for surgical treatment.

The advantages of a methodical preliminary application of ligatures to the principle arterial supply are best appreciated in the surgical treatment of the substernal, the intrathoracic, and, most of all, the very vascular exophthalmic goiter in which bleeding is persistent. These are the cases in which many surgeons hesitate to operate. Preliminary application of ligatures to the inferior thyroid arteries and to the superior poles before the veins are interfered with allows the rest of the operation to proceed without difficulty. By this procedure, venous engorgement is prevented

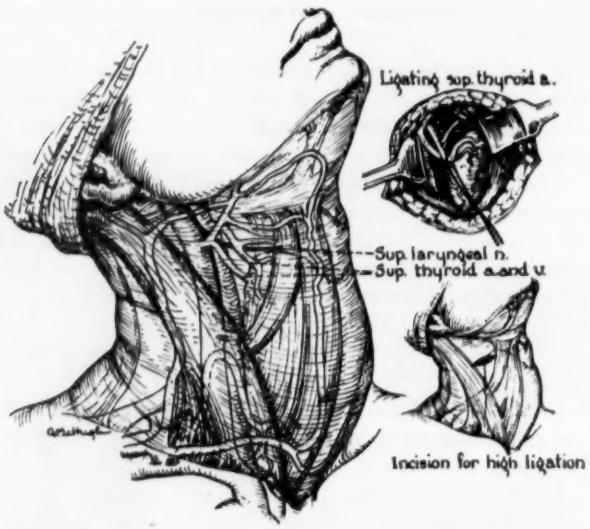

Fig. 3.—Ligation of superior thyroid artery (of value in a few adult patients with severe hyperthyroidism; especially valuable in the management of hyperthyroidism in children). (Reproduced by permission of *Surgery, Gynecology and Obstetrics.*)

and the goiter gives way easily to the pressure of the finger passed beneath the sternum. The position of the inferior thyroid artery is often much higher than normal in the retrosternal goiter because this portion is often developed at the expense of the inferior horn. Prevention of bleeding by ligation to these vessels, together with the use of intratracheal anesthesia, converts this operation into a safe procedure.

In a small percentage of cases, stage operations still have a place in the surgery of the thyroid in spite of the employment of the antithyroid drugs in the preparation of patients with hyperthyroidism. Ligation of the superior thyroid arteries is a simple, safe, and quick operation, which is followed by a marked reduction of the basal metabolic rate, as well as the pulse rate. It is a very good procedure in treating hyperthyroidism in children and in young adults and is a good barometer in these persons as to their tolerance for a later resection (Fig. 3).

SUMMARY

In the management of the patients with hyperthyroidism, as seen today, the thiourates will have a definite small place as a preoperative measure. Patients with very mild hyperthyroidism are still prepared with strong iodine solution (Lugol's solution) alone. It is evident that surgery is still the treatment of choice in the majority of patients with goiter, including those with hyperthyroidism. Surgery of the thyroid is very safe, and technical complications can usually be averted with a technique aimed mainly at hemostasis. Proper hemostasis makes possible a faster, neater, cleaner, and more practicable operation, offering better protection to the laryngeal nerves and parathyroid bodies. The great justification for the preliminary application of a ligature to the inferior thyroid artery is the simplicity and speed with which it is accomplished. It has been shown by our dissections and by others that the inferior thyroid artery is uniformly larger by one-third than the superior thyroid artery in both normal and disturbed glands. It has further been demonstrated experimentally by Enderlen and Hotz that the blood supply of the parathyroid is not interfered with, even after the ligation of all four thyroid arteries at their points of origin. Proper hemostatis prevents postoperative hemorrhage and makes possible a more rapid convalescence, a more permanent cure with much less drainage, and, as a result, a better scar.

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CORTICOTROPIN (ACTH) IN HYPERTHYROIDISM

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DURING the past two years we have had occasion to administer corticotropin (ACTH) as an adjunct to the surgical treatment of certain selected patients with thyrotoxicosis. This paper is a record of our experiences and an account of some practical and theoretical justifications for this plan of management.

Since corticotropin and cortisone have become generally available, an enormous amount of work has been done with a view to determining their influence on various disease processes. Surprisingly, in spite of the long known interrelationship between the adrenal and thyroid glands, very little has been written concerning the effect of corticotropin and cortisone on thyroid disease. This is not because surgeons are unaware of the value of these hormones. With their aid, as Hume and Moore have said, it is possible to raise to eucorticism a peripheral supply of steroids low because of endocrine disease or the increased need of tissues under excessive stress or to increase the supply of steroids in an endocrine-normal patient in hope of interfering with the natural course of a specific disease process. Cole and his associates pointed out that the temporary effect of these hormones which limits their usefulness in the field of internal medicine makes them particularly applicable to surgical problems. Moreover, their deleterious effects on fluid and electrolyte balance, wound healing, and endocrine factors, improperly called "side-effects" or "toxic reactions" (Sprague), are of no consequence during the short period of time and in the dosages which would be employed in surgery.

CORTICOTROPIN AND CORTISONE IN SURGERY

Hume and Moore have classified the surgical conditions in which corticotropin and cortisone should be of value: first, patients having frank pituitary adrenocortical failure (pituitary tumor, adrenal destruction, hypothyroidism); second, patients with relative pituitary adrenocortical deficiency (chronic exhaustion resulting from preexisting debilitating disease or prolonged and stormy convalescence, or acute deficiency following severe operative trauma, burns, cryptic shock). The improved nutritional state resulting from metabolic effects as well as from the euphoria and improved appetite and loss of malaise produced by these hormones may make a

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debilitated, inoperable patient a suitable candidate for surgery. We have had a number of critically ill, toxic, almost moribund patients in a state of chronic shock whom we were able to get into condition for operation by administering cortisone or corticotropin. Szilagyi, Margulis, and Jay have found these substances of benefit in postoperative hypotension and in hypotensive oliguria but not in hemorrhagic shock or in lower nephron nephrosis. Contraindications to their use include acute abdominal emergency (signs may be masked), peptic ulcer (activation and perforation may occur), diabetes mellitus, Cushing's disease, hypertensive cardiovascular disease, tuberculosis, and chronic nephritis. Moreover, operations are dangerous after prolonged cortisone administration because of the adrenal atrophy which develops and renders the organism incapable of withstanding additional stress.

Corticotropin and cortisone have been tried in a great many disease conditions commonly treated by surgeons. A few in which favorable results have been reported are acute bursitis, acute tendinitis, acute pancreatitis, acute parotitis, thrombocytopenic purpura, hemolytic anemia, chronic ulcerative colitis, regional enteritis, and allergic states. Their use in thrombophlebitis is sometimes beneficial, but the inci-

TABLE 1.—*General Data Concerning Patients*

Patient	Sex	Age, Yr.	Duration of Symptoms	Weight Loss, Lb.	Type of Goiter	Resting Pulse Rate	BMR
1	F	21	2 mo.	+	Diffuse	130	+ 39
2	F	20	10 mo.	15	Diffuse	120	+ 39
3	M	66	6 mo.	20	Nodular	88	+ 76
4	F	36	2 mo.	15	Diffuse	120	+ 53
5	F	39	2 yr.	6	Nodular	110	N. G.
6	F	23	4 mo.	+	Diffuse	140	+ 57
7	F	33	3 yr.	+	Diffuse	150	+ 62

dence of phlebitis is increased in patients receiving these substances and occasionally massive intravascular clotting occurs. The early enthusiasm attending their use in burns has waned but they may be beneficial in skin grafting. The decreased inflammatory reaction and fibrosis attending their use has suggested some value in prevention of postoperative adhesions. Certain infections seem to be inhibited; palliation of metastatic carcinoma is made easier, and a number of ophthalmologic problems are more readily solved with their aid.

The use of these hormones in surgery is largely empirical, based on the clinician's impression of the disparity existing between stress and reserve rather than on the results of any tests of adrenocortical activity. Sprague and his associates say there is no definite line of demarcation between the physiologic effects of corticotropin and those of cortisone. Theoretically corticotropin more closely simulates the normal pituitary adrenocortical cycle by stimulating the entire spectrum of cortical steroids. The effects of cortisone might be expected to be more limited, but its use is mandatory if the adrenal cortex proves unresponsive to corticotropin, in spite of the fact that it depresses cortical function and may produce further cortical atrophy.

In most summaries of the use of these hormones, hyperthyroidism is seldom mentioned, yet where could we have a better example of increased stress? The disease itself taxes the pituitary adrenocortical system, a system which is of importance not only in maintaining physiologic integrity but also in protecting the body

against noxious stimuli. A surgical operation is just such a stimulus and a very severe one in hyperthyroidism. Add to this the flooding of the system with thyroxin attending operative manipulation of the gland, and the stage is set for the complete breakdown of normal endocrine interrelationships clinically manifested by crisis or, as Means elects to call it, "decompensated hyperthyroidism."

THYROID-ADRENAL RELATIONSHIP

That an intimate relationship exists between the thyroid and adrenal glands has been common knowledge for many years. The adrenals may hypertrophy in hyperthyroidism, atrophy in athyrosis. Lymphoid hyperplasia is noted in both hyperthyroidism and hypoadrenalism. Thyroxin is very toxic in adrenalectomized animals or patients having Addison's disease. Hardy and his associates found decreased protein-bound iodine levels in normal or collagen disease patients receiving corticotropin or cortisone. Hill and his associates found that corticotropin and cortisone administered to patients with normal thyroid and adrenal function produced a depression of the I^{131} uptake gradient (retarding, but not completely inhibiting, the uptake). After an initial calorigenic response, the basal metabolic rate was lowered; cholesterol levels dropped; protein-bound iodine levels usually decreased. The fact that thyroid-stimulating hormone elicited a thyroid response in the presence of a high level of circulating steroids they felt indicated the effect of the hormones was one of pituitary inhibition (both thyrotrophic hormone and corticotropin). Corticotropin produced no thyroid response in patients with Addison's disease, although cortisone might. The adrenocortical response as measured by the eosinophile count and 17-ketosteroid excretion was delayed and inadequate in hypothyroidism but could be improved by thyroid extract. The adrenocortical response was normal in most patients with hyperthyroidism. They concluded that there was a close relation between the thyroid and the adrenals. Corticotropin depressed thyroid activity, with resulting decreased adrenocortical activation and decreased response to coticotropin. As a result of his experiments on rats, Perry feels that the effect on the thyroid is direct and not mediated by the pituitary. Wolfson and his associates found that giving corticotropin and cortisone produced an increase in oxygen consumption, a direct calorigenic effect not involving the thyroid because it occurred in myxedema without change of signs or symptoms. After receiving corticotropin or cortisone, 20 of 24 euthyroid patients developed decrease of thyroid function, often without change of basal metabolic rate. The glycocorticoid-induced thyroid depression they called "corticogenic hypothyroidism." The usual symptoms of hypothyroidism might be absent. Basal metabolic rate and cholesterol were not dependable indices because of the direct effects of the hormones on them; however, the I^{131} uptake was decreased within a few hours of the first dose of hormone and the protein-bound iodine levels decreased later (slow utilization of circulating thyroxin). This deficiency could result in failure of the adrenal cortex to respond to corticotropin unless thyroid extract was administered. Kuhl and Ziff, Houssay, and Salter and Rosenblum also have studied the effects of corticotropin and cortisone on thyroid function.

CORTICOTROPIN AND CORTISONE IN THYROID DISEASE

An early attempt to influence thyroid disease with adrenal preparations was that of Solis-Cohen in 1897. Marine wrote on this subject in 1922, Shapiro in 1924. Since the development of corticotropin and cortisone, a few studies have been carried

out to ascertain their effects in thyroid disease. Crile has reported prompt remission and resolution of subacute thyroiditis. Werner and his associates found that the thyroid gland in struma lymphomatosa became smaller and softer, and needle biopsy showed decreased lymphocytic infiltration. These workers also described diminished skin thickening in myxedema. Several reports (Reiss and associates, and DeCourt, and associates, Hill and associates) of decreased orbital edema in exophthalmos have appeared, an effect denied by others (Salassa, Engel, Szilagyi), but the proptosis appears to be unaffected in any event.

Hill and his associates administered corticotropin and cortisone to patients having hyperthyroidism and after a transient increase of activity observed a depression of thyroid function in one-half of their cases. The best results were obtained in disease of short duration and patients showing the greatest degree of adrenal response as measured by eosinophile depression and increased 17-ketosteroid excretion. One patient with thyrogenic thyrotoxicosis proved refractory. Reiss and his associates treated four patients having hyperthyroidism with corticotropin. They noted increased toxicity the first day. The I^{131} gradient increased. This lasted for 3 to 10 days during which the gradient and total counts fell. After this two patients exhibited marked improvement, one slight and one none. Improvement corresponded to the degree of increase of 17-ketosteroid excretion. The basal metabolic rate decreased later and the gland decreased in size in the two patients showing the most improvement. Changes in the protein-bound iodine were the most marked of all. In one case, corticotropin was the only preoperative medication given. They concluded that this was not a reliable or practical form of therapy for hyperthyroidism. Moseley and Merrill studied one patient with thyrotoxicosis and thyrotoxic heart disease and mild congestive failure. Although there was no change in his clinical status after five days on corticotropin, his basal metabolic rate dropped; his cholesterol increased, and there was a good eosinophile and 17-ketosteroid response. Engel reported on a patient whose basal metabolic rate fell from 44 to 4 in 10 days, and the edema associated with congestive failure disappeared. Rawson stated that his studies on the effects of these hormones in hyperthyroidism had not been dramatic. Werner observed no change in two patients he studied. Szilagyi and his associates have conducted a classic study. They treated three patients in crisis and found corticotropin beneficial in all, lifesaving in one, although the value of other drugs used in these cases was conceded. Five patients with severe hyperthyroidism unmanageable with conventional methods were given corticotropin; all had been given antithyroid drugs; four also received small doses of iodine. Evidence of cortical response was obtained in all cases, but its magnitude varied. Thyroid activity as measured by cholesterol, protein-bound iodine, basal metabolic rate, I^{131} uptake and excretion, was depressed in one case, slightly depressed in one case, augmented in one, and unaffected in two. Clinically the disease seemed only moderately influenced. All patients were still hyperthyroid at the time of operation, yet all stood operation remarkably well and recovery was amazingly quick. The authors conclude that corticotropin is not a useful addition to the medical treatment of hyperthyroidism, but that it is useful in crisis and a helpful agent in preparing for operation patients unaffected by conventional methods. More recently Gyulai and Szántó have recounted their experiences with corticotropin. They found it beneficial in

three cases of hyperthyroidism which they considered inoperable and they felt it most helpful in certain operable cases. Freeman and Holley treated three patients with thyroid crisis with corticotropin. There was prompt striking clinical improvement in two cases, but the third patient died. Langeron, Giard, and Nolf also have written on the subject of corticotropin in hyperthyroidism.

MODE OF ACTION OF CORTICOTROPIN AND CORTISONE IN THYROID DISEASE

Any consideration of new forms of therapy of hyperthyroidism must take into account the changing picture of thyroid disease. It seems ironical that as we physicians are acquiring more potent weapons, the disease itself is becoming attenuated. Crises are seldom encountered; stage operations are almost forgotten; critically ill thyrotoxic invalids are almost never seen. Dinsmore says that even the picture of malignancy is shifting from predominantly angioinvasive adenocarcinoma to lymphatic-invading papillary carcinoma occurring in a younger age group. Changed dietary habits, prophylactic iodine, goitrogens, and bioantagonists all play a part in the changing thyroid pathology (DeCourcy).

The manner in which corticotropin affects the hyperthyroid patient has been explained in many ways. As Reiss has said, the inconstancy and variability of the effects suggest that unknown factors may be contributing to the over-all picture. Szilagyi feels that the character of the endocrine imbalance may vary in different patients although its clinical manifestations are similar. The importance of cerebral cortex influences in producing increased thyroid activity is well known (Heinbecker). The lessened irritability and instability in treated patients added to the euphoria commonly seen during corticotropin therapy suggests a cerebral cortex effect. McGavack emphasizes the sugar-metabolism-regulating role of the adrenal cortex which is taxed to the utmost by the increased energy demands of thyrotoxicosis. He suggests that in severe cases cortisone may protect the heart and liver by improving utilization of fat and metabolism of carbohydrate. This seems a rather narrow interpretation of the effects of a substance of profound biologic significance capable of producing widespread physiologic alterations.

It seems that cortisone and corticotropin may depress thyroid function. Whether they act by inhibiting the thyrotrophic hormone (as iodine neutralizes or prevents the effect of thyroid-stimulating hormone and thus brings about involution of the gland) or by a direct effect on the thyroid gland (as the goitrogens block thyroxin formation without offering protection against or antagonism to, or preventing release of, hormone already formed) is not known.

However, the most important effects in crisis, operative reaction, and postoperative recovery may be nonspecific and simply actuated through the antistress response of the adrenal cortex to an alarm reaction. According to Szilagyi, the details of the endocrine complex manifested as thyrotoxicosis vary, but the ability of the body to meet this or any additional stress depends on the balance between the adrenocortical response and stress. If the response is inadequate, decompensation (crisis) occurs. The similarity to the stress reaction of Selye's adaptation syndrome is immediately apparent (Jahn). Corticotropin helps to restore the disturbed equilibrium. Naturally if the adrenal cortex were completely exhausted (negative Thorn test), cortisone, rather than corticotropin, would be required.

This basically is the real rationale for the use of corticotropin in hyperthyroidism. It is not a new way of treating hyperthyroidism. Iodine preparation followed by a thyroidectomy is the treatment of choice for the average patient having diffuse goiter with hyperthyroidism. Antithyroid drugs (methimazole [Tapazole] or propylthiouracil) should be used to prepare the more severe cases, with iodine administered preoperatively to bring about involution. We do not use these drugs for definitive therapy because of the high incidence of relapse (Williams), but we have found them of value for therapeutic tests. Radioactive iodine is probably the best method of dealing with diffuse toxic goiter in the aged, in patients with severe cardiac disease, or in recurrence. Toxic nodular goiter responds poorly to medical therapy, seldom recurs after surgery, may be the site of carcinoma, and therefore usually should be treated surgically (Judd). However, one encounters periodically a patient with severe thyrotoxicosis, with either a diffuse or nodular goiter, who does not respond satisfactorily to antithyroid drugs, who is iodine-fast, who frets under prolonged efforts to bring him under control, whose cardiac status is deteriorating rapidly. With the help afforded by corticotropin we can now offer this patient the immediate beneficial effect of subtotal resection with safety. Without corticotropin we would anticipate postoperative crisis or at least a very stormy course, and the risk involved by operation would be almost prohibitive. By bolstering the pituitary adrenocortical axis against the great stress imposed by surgery and the oversecretion of thyroxin, we can proceed with a degree of assurance and safety heretofore unknown.

REPORT OF CASES

CASE 1.—B. K. (1827), aged 21, a white, married woman, was first observed on Dec. 8, 1951, complaining of severe nervousness, exertional dyspnea, hyperhydrosis, fatigue, and recent weight loss. The symptoms were of two months' duration. The past medical and surgical history included only a right inguinal herniorrhaphy, uterine suspension, and removal of a right ovarian cyst.

Physical examination revealed a nervous, apprehensive young woman who exhibited bilateral exophthalmos, lid lag, and poor eye convergence. There was a diffusely enlarged thyroid gland over which a bruit was easily heard. A fine, rapid tremor of the hands and tongue was noted. There was considerable quadriceps weakness, and atrophy of the shoulder girdle muscles was observed. The resting pulse rate was 110.

The BMR was 39%, and the blood cholesterol was 188 mg. per 100 cc.

A diagnosis of Graves's disease was made, and on Dec. 10, 1951, therapy was begun with 2-mercapto-imidazole, 15 mg. daily. On Dec. 18, 1951, syrup of hydriodic acid, 15 gtt. daily, was added to the therapy. On Dec. 28, there had been only slight clinical improvement, and the BMR was +29%. On Jan. 11, 1952, the patient was hospitalized because of failure to improve. At that time the pulse rate was 120 to 140, and the BMR was +32. By Jan. 25, the patient had not responded to continued antithyroid therapy and bed rest in the hospital. The weakness, exophthalmos, and tremor were worsening, and the pulse rate was still 120 to 140. Operation was decided upon, but, as it was feared her convalescence might be complicated by crisis, she was given corticotropin. On Jan. 25, 1952, corticotropin was begun in a dose of 100 mg. I. M. daily in four divided doses.

Subtotal thyroidectomy was carried out on Jan. 28, 1952. The removed portion of the gland weighed 39 gm. and exhibited diffuse parenchymatous hypertrophy. Corticotropin was continued on the same dosage schedule through Jan. 30. On Jan. 29, an absolute eosinophile count showed no circulating eosinophiles. On Jan. 31, the dosage of corticotropin was reduced to 75 mg., and on Feb. 1 the corticotropin was discontinued.

The patient's postoperative course was smooth and uneventful except for an episode of mild tetany occurring on the day of operation, which was felt to be precipitated by hyperventilation. (Chart 1).

She was discharged from the hospital on the fourth postoperative day and has remained well since that time except for signs of mild tetany during the first three months after her operation. This situation was easily controlled by the administration of calcium and calciferol. On April 8, 1952, the pulse rate was 78, the blood cholesterol 270 mg. per 100 cc. and the BMR was —11%. She was last seen in July, 1953, at which time there was no evidence of recurrent hyperthyroidism, hypothyroidism, or residual hypocalcemia.

Case 2.—L. P. (29792), a 20-year-old white married woman, was first observed on June 16, 1953, complaining of severe fatigability since the birth of her third child 10 months previously.

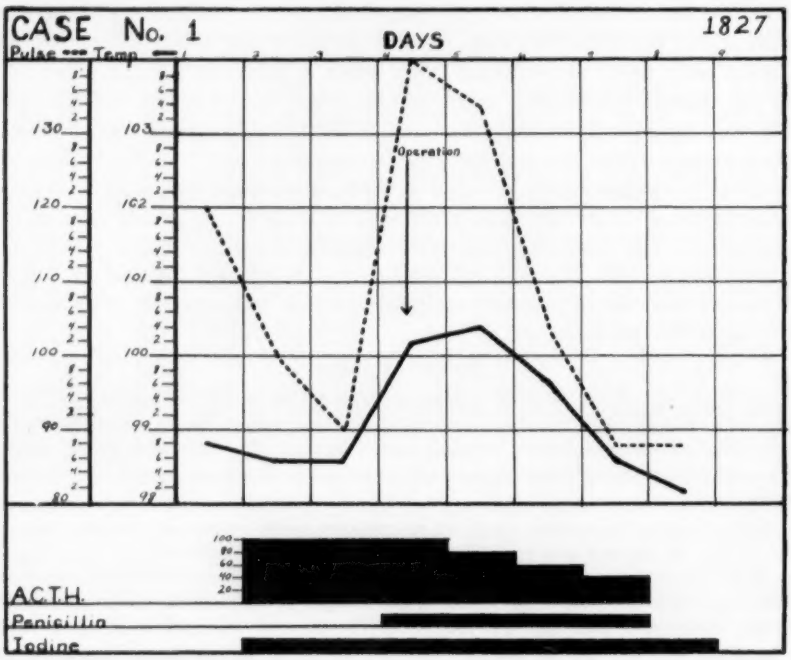

Chart 1.

There had been a 15 lb. (6.8 kg.) weight loss. She also complained of voracious appetite, palpitation, heat intolerance, sweating, and leg weakness, and noted hand tremor.

The past history was noncontributory.

Physical examination revealed a thin, nervous, poorly nourished young woman, who had a bilateral stare and slight lid lag. The skin was warm and wet. Blood pressure 120 systolic and 72 diastolic. Resting pulse rate 120. The thyroid gland was diffusely enlarged to a marked degree. The heart rate was regular, and a soft, systolic apical murmur was heard. There was bilateral quadriceps weakness. A tremor of the hands was noticed.

Laboratory studies were within normal limits except for the BMR, which was + 39%.

A diagnosis of Graves's disease was made, and she was given syrup of hydriodic acid, 15 gtt. daily. Early thyroidectomy was elected because of the severity and seeming rapid progression of her thyrotoxicosis. On June 26, 1953, subtotal thyroidectomy was carried out, removing 41 gm. of tissue which exhibited diffuse parenchymatous hypertrophy and lymphocytic infiltration.

On the day of surgery, she was given 120 mg. of corticotropin I. M. in six divided doses. On the first postoperative day the dose was reduced to 80 mg., and it was further reduced to 60 mg. on the third postoperative day and discontinued on the fourth postoperative day; afterward the patient was discharged from the hospital. The postoperative course was remarkably smooth (Chart 2). On July 6, 1953, two weeks after her operation, she had gained 10 lb. (4.5 kg.) and felt exceptionally well. She was last seen in November, 1953, has remained well, and gained a total of 22 lb. (10 kg.).

CASE 3.—L. H. (29467), a 66-year-old white man, was first observed on May 21, 1953. He complained of nervousness, palpitation, excitability, and 20 lb. (9.1 kg.) weight loss despite a good appetite. His symptoms were of six months' duration. He had noted the presence of a goiter for a long time.

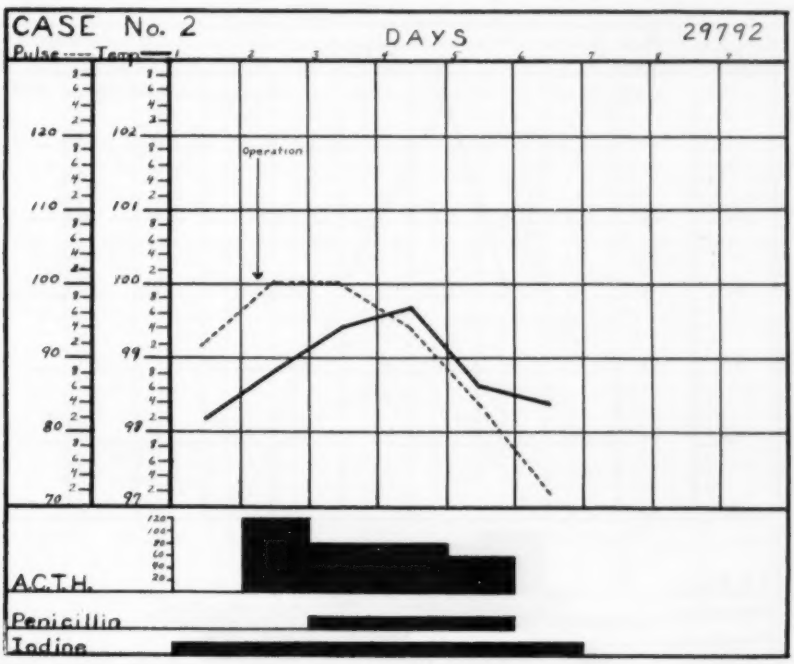

Chart 2.

He stated that in 1908 he had had pulmonary tuberculosis with a right hemopneumothorax with no sequela. In 1911 he developed primary syphilis, which was treated with arsphenamine and mercury injections.

Physical examination revealed a very tense, elderly man, who was poorly nourished and showed evidence of recent weight loss. There was no lid lag or exophthalmos. The blood pressure was 160 systolic over 82 diastolic. The radial pulse rate was 88; the rhythm was regular. An irregular, nodular goiter was present. A fine, rapid tremor of the outstretched hand was noted.

Significant laboratory studies included a blood Kahn test, which was negative, a blood cholesterol of 120 mg. per 100 cc., BMR's +88 and +76. The I^{131} uptake was 76% of the ingested dose in 24 hours. An x-ray of the chest revealed deviation of the trachea to the right, calcification in the aorta, and pleural thickening at the right lung base.

A diagnosis of toxic, adenomatous goiter was made, and on May 26, 1953, therapy was begun with iothiouracil (Itrumil), 200 mg. daily. One week later, he seemed improved. The blood pressure had fallen to 120 systolic over 70 diastolic, and the pulse rate was 76. On

June 9, 1953, after two weeks' treatment, he was more tense and nervous than previously; the hand tremor had increased, and the pulse rate was again 88. On this date the iothiouracil was increased to 300 mg. daily. On June 19, 1953, the BMR was +62 and the patient appeared unimproved. Strong iodine solution, U. S. P. (Lugol's solution), 15 gtt. t.i.d., was added to the therapy. On June 25, his symptoms were unaltered, and the pulse was rapid and completely irregular. An electrocardiogram at that time revealed auricular fibrillation. He was digitalized, and in 48 hours the auricular fibrillation had reverted to a normal sinus rhythm.

After six weeks of observation, there was no apparent response to antithyroid therapy. On July 1, 1953, subtotal thyroidectomy was carried out, and a large, adenomatous goiter was removed. The right lobe weighed 60 gm., the left lobe 15 gm. Because of the severe thyrotoxicosis which could not be brought under satisfactory control, he was given corticotropin

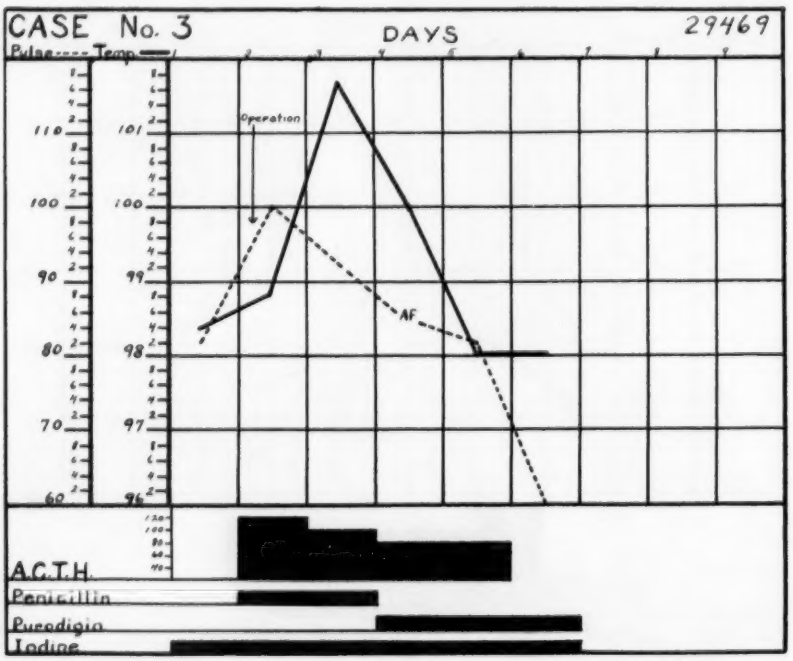

Chart 3.

postoperatively, beginning with 120 mg. on the day of operation, with a gradually decreasing dosage to 60 mg. on the third postoperative day, with discontinuation of corticotropin on the fourth postoperative day. His course in the hospital following operation was uneventful except for a very brief episode of auricular fibrillation on the second postoperative day with reversion to normal rhythm spontaneously (Chart 3). He was discharged on the fifth day.

He subsequently discontinued digitalis without further disturbance in the cardiac rhythm. When last seen on Oct. 5, 1953, he had gained 20 lb. (9.1 kg.) and felt well in every respect.

Case 4.—R. Z. (28049), a 36-year-old white, married woman, was first observed on Feb. 10, 1953. She stated that she had been well until two months previously when she had had the "flu." Since that time she had noticed palpitation, increased nervousness, air-hunger, and 15 lb. (6.8 kg.) weight loss, despite a good appetite, profuse sweating, and considerable weakness.

The past history was not unusual except that she had been told she had had a low metabolic rate several years previously.

Physical examination revealed a nervous, anxious, middle-aged woman, whose eyes were slightly prominent. The skin was warm and moist. There was a marked tremor of the hands, and frequent purposeless movements were noted. Grade III diffuse enlargement of the thyroid gland was observed. The blood pressure was 126 systolic over 70 diastolic, temperature 99 F., pulse 120, regular and forceful. The deep tendon reflexes were generally hyperactive, and considerable quadriceps weakness was present.

Laboratory determinations were not unusual except that the basal metabolic rate was +53% on one occasion and +51% on another. A chest x-ray was negative except for some fullness in the region of the pulmonary artery of questionable significance. An electrocardiogram revealed only sinus tachycardia.

A diagnosis of Graves's disease was made, and on Feb. 10, 1953, therapy was started with iothiouracil (Itrumil), 300 mg. daily. On March 16, 1953, five weeks after beginning therapy,

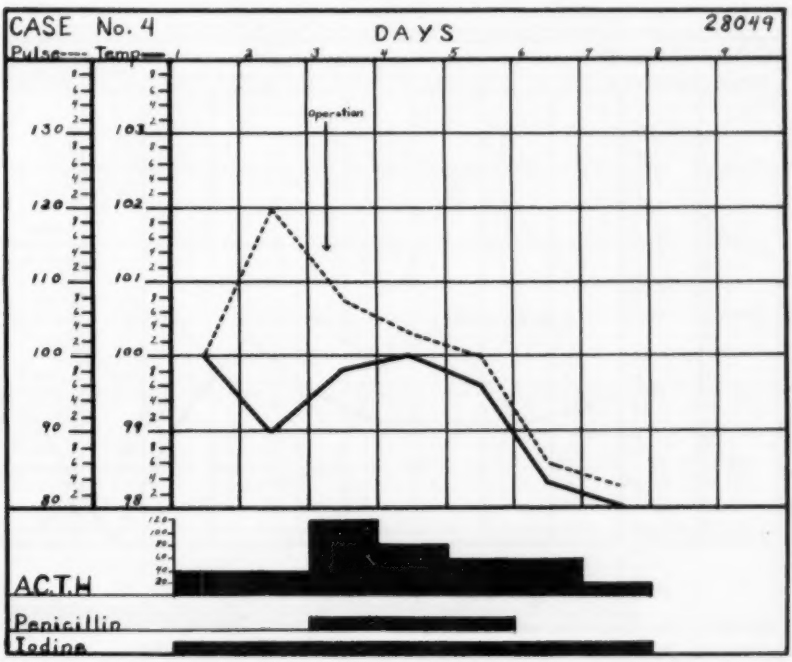

Chart 4.

there had been only slight improvement and on that date the patient was started on strong iodine solution, U. S. P., 15 gtt. t. i. d. On March 23, the patient was hospitalized because of continuous tachycardia and other evidence of continued, severe thyrotoxicity. Because of the poor response to antithyroid medications, surgical treatment was elected, and on the morning of March 25, 1953, an anesthetic was administered on the ward and subtotal thyroidectomy was carried out. The gland weighed 85 gm. and on section revealed diffuse parenchymatous hypertrophy and marked lymphocytic infiltration.

Corticotropin (Acthar Gel), 40 mg. was administered for two days prior to operation and on the day of operation, 120 mg. of corticotropin in divided doses was given intramuscularly. The dose was gradually decreased to a single 20 mg. injection on the fourth postoperative day. The patient withstood the operative procedure very well and her postoperative course in the hospital was entirely uneventful (Chart 4). She was discharged on the fourth postoperative day. The patient remained well, and on May 28, 1953, it was felt that there were

signs suggestive of slight hypothyroidism, which was subsequently treated with thyroid substance, ½ grain (0.03 gm.) daily. When last seen on July 28, 1953, the patient had regained her normal weight and was entirely asymptomatic.

CASE 5.—R. K. (25273), a 39-year-old, white, married woman, was first observed on Sept. 12, 1952. She complained of marked nervousness, emotional instability, tremor, palpitation, heat intolerance, and excessive sweating. The symptoms had been present for two years but had been considerably aggravated in recent months during which time there had been a weight loss of 6 lb. (2.7 kg.). In addition, the patient admitted that she had frequently used alcohol to excess during the past year. The past history was noncontributory.

Physical examination revealed a nervous, emotionally unstable, middle-aged woman with mild bilateral exophthalmos. The skin was warm and moist. There was a diffuse, Grade II enlargement of the thyroid gland. A marked tremor of the outstretched hand was noted. There was no quadriceps weakness.

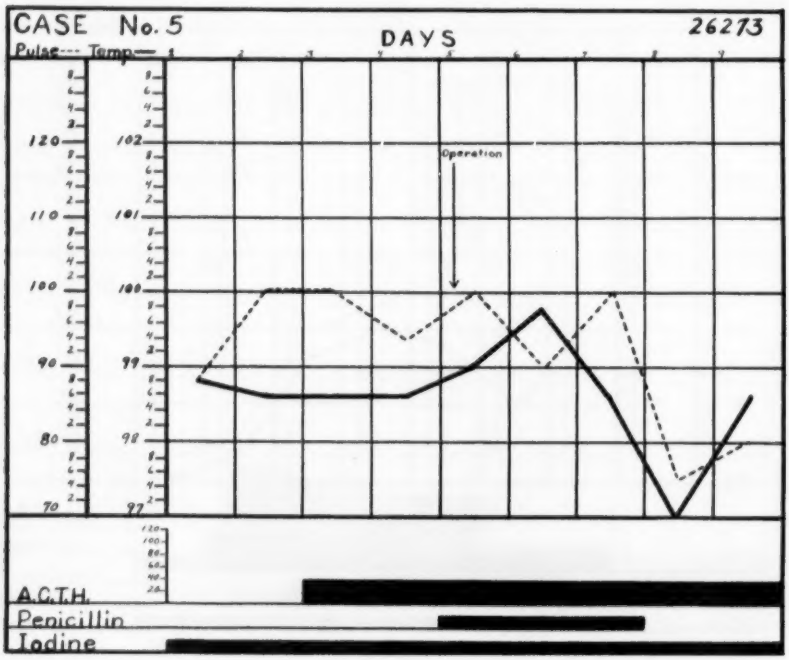

Chart 5.

Routine laboratory studies were within normal limits. The blood cholesterol was 160 mg. per 100 cc. Basal metabolic rate determinations were attempted on several occasions but were not helpful because of the patient's inability to cooperate; the I^{131} uptake was recorded as 56% of the ingested dose in 24 hours. A chest x-ray was negative. On Sept. 15, 1952, a diagnosis of Graves's disease was made, and therapy was begun with 2-mercapto-imidazole, 20 mg. daily. One week later, the dose was increased to 40 mg. daily and syrup of hydriodic acid, 5 gtt. t. i. d., was added. After three weeks of therapy the patient had not improved; she had developed bilateral periorbital edema, and emotional instability was increasing. The pulse rate remained in excess of 110.

Because of the failure to respond to medical management and the rapidly increasing emotional instability, surgical treatment plus corticotropin therapy was elected. On Oct. 6, 1952, subtotal thyroidectomy was carried out. An adenomatous goiter weighing 27 gm. was removed. Cortico-

tropin (Acthar Gel), 40 mg., was administered, a single I. M. injection being given on each of two days prior to operation and on three days postoperatively. The postoperative course was smooth and without unusual event (Chart 5). The patient was discharged on the fourth postoperative day.

The patient subsequently exhibited striking improvement in her general condition and remained well for one year. Two months after operation she exhibited signs and laboratory evidence of mild hypothyroidism which responded to thyroid substance, 1 grain (0.06 gm.) daily. She used no alcohol until September, 1953, when she developed a severe anxiety reaction with a subsequent depression and again resorted to the frequent use of alcohol.

CASE 6.—P. J. (28625), a 23-year-old white, married woman, was first observed on March 24, 1953. She complained of severe nervousness, excitability, exertional dyspnea, palpitation, increased appetite, heat intolerance, and marked hand tremor. These symptoms were of four months' duration. The past history was noncontributory.

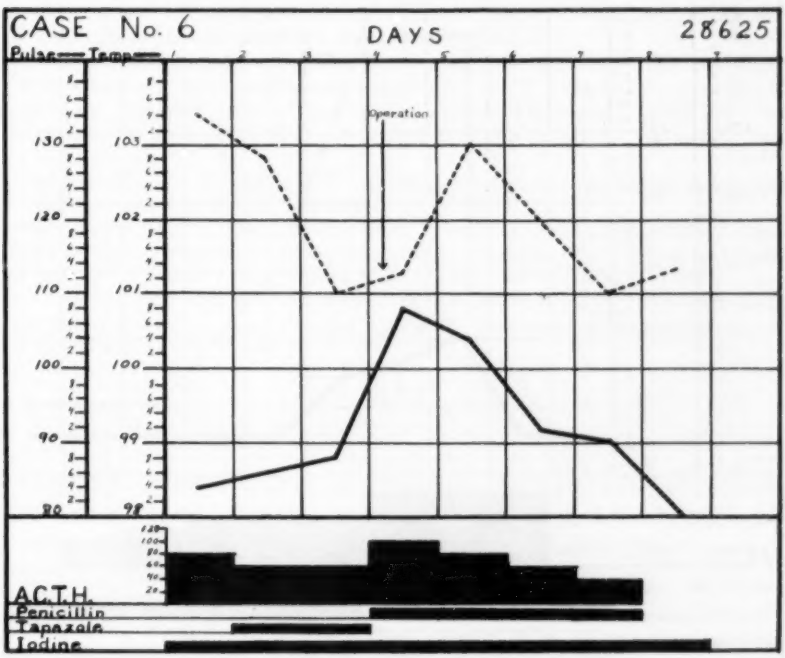

Chart 6.

Physical examination revealed a very nervous, excitable young woman, who appeared acutely ill. The skin was warm and wet, the thyroid gland enlarged, and a bruit was heard. The blood pressure was 146 systolic over 70 diastolic. The pulse rate was 144 with a regular rhythm. A marked tremor of the outstretched hands was present. Bilateral quadriceps weakness was noted. The deep tendon reflexes were generally hyperactive.

Routine laboratory studies were within normal limits. The blood cholesterol was 105 mg. per 100 cc.; the BMR was +51 and +57%.

A diagnosis of Graves's disease was made, and on March 25, 1953, therapy was begun with 2-mercapto-imidazole, 25 mg. daily. After one week this dosage was increased to 40 mg. daily and syrup of hydriodic acid, 5 gtt. t. i. d., was added. One week later the patient had developed nausea, vomiting, and constant diarrhea. She was hospitalized at this point and kept at bed rest. The gastrointestinal symptoms were treated symptomatically and antithyroid therapy was continued as above. On April 12, 1953, therapy was begun with corticotropin (Acthar Gel),

40 mg. daily. However, the patient continued to appear markedly stimulated, and the pulse rate averaged 140 to 160. On April 15, 1953, subtotal thyroidectomy was carried out and an unusually vascular, diffuse goiter was removed, which weighed 35.5 gm. On section the gland revealed diffuse parenchymatous hypertrophy and lymphocytic infiltration. On the day of operation 100 mg. of corticotropin in five divided doses was administered, and the dosage was gradually decreased to 40 mg. in two divided doses on the third postoperative day. Corticotropin was subsequently discontinued. The postoperative course was uneventful, except that tachy-

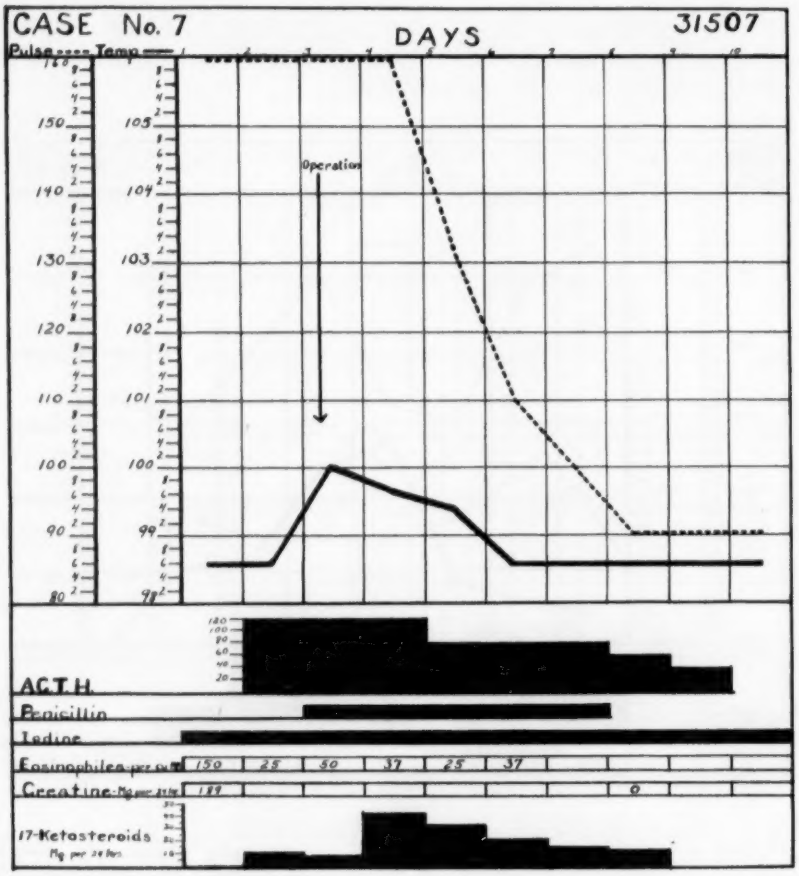

Chart 7.

cardia persisted although to a slighter degree (Chart 6). During the next three months the patient gained 16 lb. (7.3 kg.) and noted a rapid increase in strength and sense of well-being. When last observed, on Sept. 4, 1953, she was entirely asymptomatic and euthyroid.

CASE 7.—R. S. (315070), a 33-year-old, white, married woman, was first observed on Nov. 5, 1953. She had been well until three years previously, when she noted the presence of a goiter accompanied by increased nervousness, weight loss, excessive appetite, sweating, weakness, and hand tremor. At that time a physician in Georgia began treatment with propylthiouracil, 300 mg. daily. Her symptoms improved and she continued this treatment for two years until September, 1952, when her symptoms recurred. At that time she had moved to

Washington and was seen by another physician, who discontinued the propylthiouracil and began treatment with strong iodine solution, 20 gtt. daily. This medication did not improve her symptoms, but she continued to take it until she was first seen here in November, 1953.

Physical examination revealed a well-nourished, middle-aged woman who appeared ill. There was slight bilateral exophthalmos and slight lid lag. No convergence weakness was elicited. Generalized sweating was noted. There was a large, diffuse goiter over which a bruit was easily heard. Blood pressure was 150 systolic over 72 diastolic. The pulse rate varied from 140 to 160 per minute. Rather marked atrophy of the shoulder girdle muscles and the temporal muscles was noted. Moderate quadriceps weakness was present. A fine, rapid tremor of the hands was noted.

Significant laboratory studies included a BMR of + 62%. The blood cholesterol was 80 mg. per 100 cc. Creatine excretion in 24 hours was 189 mg.; 17-ketosteroid excretion was reported as 13 mg. in 24 hours.

Because of the lack of response to long-continued medical therapy, the very toxic state of the patient, and previous experience with combined corticotropin and surgical treatment in similar cases, this form of treatment was elected for this patient.

She was hospitalized on Nov. 9, 1953, and treatment with corticotropin, 120 mg. daily in six divided doses, was begun 24 hours prior to surgery. On Nov. 11, 1953, a thyroidectomy was carried out. The dissection was difficult; however, the patient tolerated the procedure well. The micropathology report was diffuse parenchymatous hypertrophy of the thyroid gland, weight 69 gm.

Corticotropin therapy was continued for a period of six days, and the patient's postoperative course was quite smooth and without unusual event (Chart 7).

Because of the patient's prolonged toxic state, it was considered possible that she might have some degree of adrenal cortex exhaustion. It therefore seemed wise to obtain an objective measurement of her adrenal cortex response to stimulation with corticotropin. For this reason, daily eosinophile counts and daily measurement of the 17-ketosteroid excretion were carried out. The results of these studies are recorded in Chart 7. The adrenal cortex response measured in this fashion was entirely adequate.

COMMENT

It will be observed that in general the foregoing cases presented certain features in common. With one exception all were suffering from moderate to severe hyperthyroidism. The exception was the patient in whom the picture was confused by the associated presence of alcoholism. Often the clinical severity of the disease seemed more marked than the basal metabolic rate indicated. None of the patients responded satisfactorily to conventional management. Some exhibited initial improvement only to deteriorate later. In one case prolonged definitive conservative therapy had been attempted elsewhere. Fibrillation began in one patient while he was under intensive therapy. One developed a gastrointestinal crisis which interfered with the continuation of the program. In one, the rapid fulminating progression of the disease seemed a contraindication to prolonged therapy. It is possible that in some of these patients prolonged persistance in conservative therapy might ultimately have resulted in improvement, but the immediate benefits available from thyroidectomy, if it could be performed with safety, proved too strong a temptation to resist. It must be admitted that in our first case operation was carried out with considerable trepidation, yet the smooth postoperative convalescence proved our fears groundless. These were all patients about whom we were very much concerned. They were persons in whom we would have anticipated a crisis or at least a very stormy convalescence under ordinary conditions. There is no test by which such cases can be singled out. It is entirely a matter of experience and clinical judgment, but in our opinion they were all doing badly and would have had a rough time of it after operation without additional help.

Yet all of these patients stood the actual operative procedure very well and all had amazingly smooth postoperative courses. The only complications were mild, transient tetany in one patient and one day of auricular fibrillation in the old man in whom fibrillation occurred preoperatively. Since all of these patients had received conventional therapy, antithyroid drugs and/or iodine and other supportive measures, one may well ask if their smooth course cannot be attributed to these measures. Would they not have done just as well without corticotropin? This would be hard to prove even with a carefully controlled series. All that we can say is that these patients were not doing well on the drugs they were getting before we decided on the operation-corticotropin program.

TABLE 2.—*Preoperative Consideration*

Patient	Duration of Medical Treatment	Reason for Departure from Conventional Therapy
1	7 wk.	Deteriorating rather than improving (H)
2	10 days	Severe disease in 20 yr. old para III; remote residence; economic factors
3	6 wk.	Deteriorating rather than improving; auricular fibrillation
4	6 wk.	Questionable improvement (H)
5	3 wk.	Increasing instability; lid edema
6	3 wk.	Gastrointestinal crisis (H)
7	3 yr.	Severe persistent hyperthyroidism (H)

(H) indicates hospitalization was part of medical management.

TABLE 3.—*Postoperative Complications*

Patient	Immediate	Late
1	Mild tetany	Transient mild tetany
2	None	None
3	Auricular fibrillation	None
4	None	Transient mild hypothyroidism
5	None	Transient mild hypothyroidism
6	Tachycardia	None
7	Tachycardia	None

At first we thought it might be necessary to give corticotropin for a considerable period preoperatively. This would certainly be true if one were attempting to influence the hyperthyroid state, but this was not the effect we sought. We were primarily interested in the antistress effect of corticotropin, an effect manifested almost immediately after adminstration of the hormone, provided the adrenal cortex is still responsive. Therefore, it was only necessary to administer it in the operative and immediate postoperative period. Occasionally, we gave it for a day or two before operation, but our greatest reliance on it was during and after operation. It was our feeling that if we were fortunate enough to get some antithyroid effect as well, it was something that was thrown into the bargain and was strictly a bonus for which we were duly grateful, but on which we were not relying. Once the danger of crisis was thought safely past, the drug was gradually discontinued. We believe that prolonged attempts at achieving euthyroidism in an unresponsive, seri-

ously ill thyrotoxic patient are no longer justified. To persist for month after month with a sick and unhappy patient who must be followed closely with frequent office visits and laboratory tests, who feels terrible and is unable to keep house or earn a living, is economically unsound and inhuman if operation can offer prompt relief safely. Formerly such efforts were praiseworthy, in fact, essential. But corticotropin has changed the picture, and as soon as progress by conventional methods ceases operation supplemented by corticotropin should be considered.

SUMMARY AND CONCLUSIONS

Corticotropin and cortisone have proved useful adjuncts in the management of many surgical problems. An intimate relationship exists between the thyroid and adrenal glands. Corticotropin and cortisone have been tried in various forms of thyroid disease by numerous investigators. The effects of corticotropin described in hyperthyroidism are largely due to broad antistress effects, although the drug may offer some specific antagonism to thyroid and/or pituitary function. It is useful in the management and prevention of thyroid crisis and is a valuable adjunct to surgery in patients with hyperthyroidism failing to respond to conventional management. Seven illustrative cases have been presented.

DISCUSSION

DR. WILLARD BARTLETT, St. Louis: This subject is a happy hunting ground for all of us who like to reminisce.

In our vicinity, it seems to have become fashionable among a generation of surgeons younger than I to do routinely a total thyroidectomy for toxic goiter. I think this is a poor way of acquiring experience with surgery of goiter for those who are relatively inexperienced. To me, the classic study on the technique and the results of total thyroidectomy in a large number of patients was made about five years ago by Arthur Scott of Temple, Texas, whom many of you know well. I discussed this with him only yesterday, in St. Louis. I am prompted to speak of it here, to remind you that he—a surgeon of very large experience over a period of 20 or 25 years in subtotal thyroidectomy—undertook to do total thyroidectomy for exophthalmic goiter in the early 1930's. In the study to which I refer, he reported the results on his first 300-odd thyroidectomies. His percentage of complications resulting from technical errors in performing the operation was much larger in his first hundred than it had been with subtotal thyroidectomy. In his second hundred total thyroidectomies, he reduced the incidence of nerve and parathyroid injuries almost to that which he had had previously in doing subtotal thyroidectomies. In his third hundred total thyroidectomies, he got his percentage of such complications below that which he had in performing subtotal thyroidectomies.

I submit to you that the surgeon who starts doing total thyroidectomies with a very small background of experience—who is an occasional operator on the thyroid gland, and perhaps, by interest or opportunity, will remain so—will have an experience with total thyroidectomy that is going to be hazardous for the patient for many years to come. If he does only 10 or 12 a year, it will certainly take him a long time to get his first hundred "totals" done.

Now, I have raised this point with some of my own young colleagues, and I hope you will repeat it in speaking to some of the men coming along who are deeply interested in this field but who have only a small experience in it. I hope, too, that you will be more fortunate than I have been in inducing any of them to change their minds, because I am regularly greeted with a speech in response, telling me how wrong I am in my appraisal of the situation.

DR. ARNOLD JACKSON, Madison, Wis.: Yesterday I arose to express my confusion as to the proper technique in gastric resection. I am sure that some of you who are not especially interested in the field of thyroid surgery must have undergone the same doubt and confusion in your minds as to the proper method of treating hyperthyroidism.

We know we can abate hyperthyroidism by radioactive iodine, by thyroidectomy, by antithyroid drugs, and now, possibly, by corticotropin. We know we can do a good thyroidectomy by exposing the recurrent laryngeal nerves, by tying the inferior thyroid artery, or without doing that. The main thing is to do a good operation.

May I express my appreciation to Dr. Nordland? I have seen him operate, and he does a most skillful thyroidectomy.

During the past year, several of us interested in the field of thyroid disease have been trying corticotropin in the treatment of acute thyroiditis, but this report of Dr. Schlicke is the first I have heard on the treatment of hyperthyroidism.

However, one must question the necessity of using corticotropin in the treatment of hyperthyroidism, and particularly as it relates to crises. The latter have become even more scarce than croup and typhoid fever.

In 1927, I published in *Surgery, Gynecology and Obstetrics* a report of 120 cases in which primary thyroidectomy for exophthalmic goiter was performed, thus eliminating the necessity for the ligation operation. All of these cases were perfectly controlled with strong iodine solution, U. S. P. (Lugol's solution). No crises were observed, or have since been seen, except in those patients who were iodine-fast. The discovery of thiouracil in 1943 by Astwood and his coworkers, and, subsequently, the other antithyroid drugs, not only solved the problem of these iodine-fast cases of exophthalmic goiter but entirely eliminated the reaction following thyroidectomy for toxic nodular goiter.

Thus, any case of toxic goiter that is properly prepared with strong iodine solution, U. S. P., or an antithyroid drug—depending on the type of goiter—should have no crisis or severe reaction following thyroidectomy.

Dr. Schlicke has suggested a form of therapy that might prove as effective as our present methods, but I believe it offers no advantage and might possibly cause harm in some instances.

DR. B. MARDEN BLACK, Rochester, Minn.: Since I have had no experience whatsoever in treating hyperthyroidism with cortisone or corticotropin, I cannot discuss Dr. Schlicke's presentation.

I think it is true, as Dr. Jackson mentioned, that crisis has become very much a rarity since the availability of radioiodine. One can frequently avoid the entire problem by treating extremely ill patients with radioiodine or at least by nonsurgical means.

It has been thoroughly established, as Dr. Schlicke mentioned, that such drugs will control the symptoms of acute, diffuse thyroiditis. Both Werner and our group have found, however, that apparently they do not particularly influence the course of the disease. So long as the hormone is continued, the pain and tenderness are controlled; as soon as the drug is discontinued, the pain recurs. I do not believe the course of the disease is changed.

Dr. Nordland has emphasized one of the most important technical aspects of thyroidectomy. It is almost incredible that the importance of early ligation of the inferior thyroid artery has not been stressed more in the last 30 years. In addition to diminishing the blood supply to the lobe, the position of the artery is an extremely satisfactory landmark, indicating the position of the recurrent laryngeal nerve. As the artery approaches the thyroid, it divides into its terminal branches. The inferior laryngeal nerve courses either just anteriorly to the branches, between the branches, or runs in the tracheoesophageal groove where it is out of harm's way. Once the artery has been found, either the position of the nerve is known or the nerve cannot, for practical purposes, be injured. It is obviously safer to ligate the artery than to dissect out the nerve. I am very confident that if the artery were ligated routinely before resection of the lobe, fewer inadequate thyroidectomies would be carried out and injuries to the nerve would be minimized.

DR. CLAUDE J. HUNT, Kansas City, Mo.: This has been a very interesting paper upon the anatomy and the problems related to thyroid surgery. The instance of cancer of the thyroid gland is a controversial one. There are many who express themselves as being very doubtful concerning the frequency of cancer of the thyroid because, they state, in their practice they see very few cancers. I have heard that many times from the platform of the American Goiter Association. Yet, on the other hand, there are many very excellent scientific investigators whose statistics cannot be doubted who present a very high instance of cancer of the thyroid in discrete nodular goiter. For example, Drs. Cole and Crile have a percentage that varies from 17 to 22% in discrete nodular goiters. We found 11 malignant cases in 100 thyroidectomies for nodular

goiter of the discrete type. However, I do not believe a nodule is always discrete. There are usually some small adenomas or nodulations that are associated with the discrete one; therefore, it makes the gland not really a discrete nodular goiter.

In the 100 cases that we had, the age varied from 19 to 71; 7 of them were in the younger age group between 19 and 29 years. It is, however, of sufficient frequency so that one should advise always the surgical removal for a discrete nodular goiter. One never knows whether the lesion is malignant or not. Therefore, operation should be done on the basis that it is already malignant.

I believe that if the lesion is still confined to the gland, a simple unilateral total thyroidectomy with the removal of the isthmus is sufficient, especially if it is a papillary adenocarcinoma and the capsule is still intact.

There are some problems relative to the technique of thyroidectomy that were mentioned by Dr. Nordland and emphasized by Dr. Black. I agree with Dr. Black that ligation of the inferior thyroid artery outside the gland is a very satisfactory procedure. It in no way impairs the blood supply to the parathyroid glands. We have done it on many occasions but do not do it routinely. It certainly reduces the vascularity of the gland, and if the gland is inclined to be very vascular, I think this should be done.

One important thing about ligating the superior thyroid artery is that one does not make a wide sweep and enclose within the ligature the superior laryngeal nerve. The superior laryngeal nerve has two factors: one is a motor that supplies the cricothyroid muscle; the other is sensory, and it supplies the mucous membrane of the larynx. If this nerve is damaged in the ligation of the superior thyroid artery, there will be an alteration of the voice; many who are public speakers and singers will complain that their voice is impaired.

This impairment is not due to vocal cord paralysis, as the cords will move adequately and on inspection one can say that there has been no damage to the cord, but the damage to this nerve will produce a paralysis of the cricothyroid muscles and atrophy of the mucous membrane of the larynx, with a resulting dry larynx which alters the voice.

We have for years made it a policy in all thyroid operations to expose the recurrent laryngeal nerve, and we have kept definite records concerning the feasibility of this procedure.

We inspect all cords before operation and after operation, and therefore, we have definite statistical records to the effect that we have reduced nerve injury to 1% or less by this procedure. It is not difficult to expose the recurrent laryngeal nerve and we have found it misplaced in many instances. Had we not found it to be misplaced by exposure, we would have damaged it.

The nerve usually divides before it enters into the larynx; sometimes it divides a considerable way down and one or other of the divisions of the recurrent laryngeal nerve may be damaged if it is not adequately exposed. The nerve is usually damaged near the point where it enters the larynx and not well down in the trunk. It is damaged by ligature or suture.

I am glad this paper has been presented by Dr. Nordland. It is very interesting to me because of the interest I have had in the field of thyroid disease for so many years.

DR. ALFRED MCK. LARGE, Detroit: I would like to confine my remarks to studies not quite similar to Dr. Schlicke's, but in the same general vein.

Recently at the thyroid clinic of the Wayne University College of Medicine we have treated approximately 200 hyperthyroid patients with methimazole (Tapazole) and have been able to reduce the BMR and eliminate the symptoms of hyperthyroidism in all those patients. I say "all of them," but that is not quite true. Shortly before coming here I found that we had recently encountered one patient who was not controlled on 120 mg. of methimazole a day. However, with all the others, it has been possible to control them with the use of this antithyroid preparation.

Sometimes it has taken a lot more of the drug than we usually employ, up to 100 mg. or more a day, and sometimes it has taken six months or more to do it, but in this series of cases there have been no postoperative thyroid crises, and we feel that the reason for that, of course, is that it has been possible to control the hyperthyroidism before operation.

During the last five or six years, we encountered 10 cases of spontaneous thyroid crisis in Detroit, either coming on truly spontaneously or occurring in patients who had not followed medical advice in peroperative treatment, those who had stopped taking the antithyroid drugs and then had had severe exacerbations, with crisis. In those 10 patients we have been quite satisfied with the current conservative methods of management of the crisis and have felt without much question that cortisone has been a useful adjunct in the treatment of these patients.

DR. MARTIN NORDLAND, Minneapolis: As emphasized by Dr. Black, proper hemostasis is important in all thyroidectomies, but it is especially of value in the surgery of hyperthyroidism in which speed is very important.

Dr. Hunt's discussion touched upon a very important problem in thyroidectomy which is often lost sight of. The recurrent laryngeal nerve enters the larynx at the junction of the cricoid and thyroid cartilage. When a ligature is passed around the superior pole at this level, the recurrent nerve may be included, with a resulting cord paralysis. In a similar way, the superior nerve may be included in the tie. It is known that the internal branch of the superior laryngeal nerves are sensory to the mucous membrane of the larynx. The external branch, however, is motor to the extralaryngeal muscles. Injury to this branch will cause paralysis of the extralaryngeal muscles involved, causing a change of the voice to a lower pitch because of the relaxation of these muscles.

A technique based on the anatomy involved will most often avoid all the complications of thyroidectomy.

DR. C. P. SCHLICKE, Spokane, Wash.: I hope Dr. Bartlett did not get the impression from me that I was plugging totals. I do not do totals for benign disease.

Dr. Jackson raised a most important point: Is there any need for the type of therapy which I described? I certainly feel that it is important to find out what the influence of this type of hormone is on thyroid disease, and a study such as this helps contribute some light on the subject. I submit further that there are some patients whom it is very difficult to prepare by the methods we have been using in the past.

We grant that the vast majority respond very nicely to conventional methods, but we have had some that just did not seem to do very well with anything we tried.

I was very much interested to hear Dr. Large's experience. He mentioned one case in which they had persisted for six months in attempting to get the patient euthyroid. I feel that if there is a method by which one can operate safely on a patient after six weeks or so who is not doing well, then why keep him in that condition and subject him to all that discomfort and trouble for another five months? I just hope more people will try it and see if their experiences are similar to ours.

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TREATED COMPARED WITH UNTREATED BREAST CANCER

One Hundred Cases of Fischel's vs. One Hundred Cases of Daland's

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AND
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HALSTED'S radical mastectomy has been condemned by some as incapable of curing cancer. McKinnon,[1] for instance, has urged surgeons to reappraise their results from mastectomy after the pathologist has eliminated all "borderline cancer" from the surgical series. Accordingly, a group of pathologists, comprising Pinkerton,* Orrahood, Blumenthal, Wyatt, and Rice, eliminated from 100 surgical cases originally diagnosed as "carcinoma" 6 as "borderline cancer" with a 7th as lymphosarcoma, and then substituted for the 7 cases eliminated the next 7 successive cases of verified infiltrative carcinoma. There resulted 100 cases which represented successive private patients at Jewish Hospital who had all undergone radical mastectomy of Halsted's type by Fischel † or Keyes from 1928 to 1944 ‡; 34 of the 100 patients had also had postoperative irradiation and some of them had received hormones. Ten-year follow-ups were available on 90 of the 100 patients, and Fischel's 10 unfollowed patients were classified as dead as of the date of the last follow-up.

Next, Fischel's 100 radically treated patients were compared with Daland's 100 untreated patients who had died of breast cancer up to 1927 at Huntington or Good Samaritan Hospital in Boston. Although Daland [2] obtained histological verification of the diagnosis of breast cancer in only 11 of his 100 patients, his series was nevertheless chosen to represent the outcome of untreated breast cancer because the time of survival of his patients, namely, three years five months, averaged only two months above the average survival time of 777 untreated patients with breast cancer reported in the literature.[3] Furthermore, Daland studied untreated breast

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* Professor of Pathology, St. Louis University School of Medicine.

† Dr. Fischel died May 12, 1938.

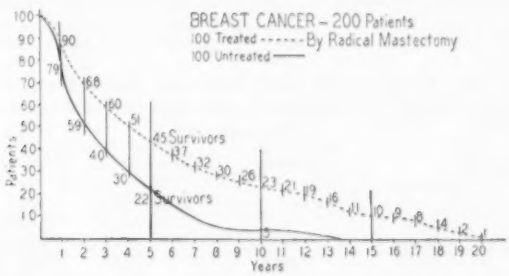
‡ Fischel's 100 patients were chosen, and 165 other private patients were rejected from 1928 to 1944 because 129 were treated elsewhere than at Jewish Hospital or by operations not Halsted's; 22 because the cancer was inoperable when first seen, 7 because the tumor was not carcinoma (see text), 5 because the original slides were lost, and 2 because frozen section diagnosis was not verified by paraffin sections. Of the 22 inoperable patients, 14 were prorated to use with Fischel's 100 treated patients.

cancer to furnish a basic series for comparison with the teated series, in order to evaluate the effectiveness of radical mastectomy. He included in his series only patients who had died of breast cancer and omitted from his series one woman, still living with one breast destroyed by cancer of 36 years' duration, only because she had not yet died.

RESULTS

As compared with three years five months, the survival time of Daland's untreated patients, Fischel's treated patients survived for six years one month after onset. Hence mastectomy almost doubled their life span. Furthermore, 21 of Fischel's 100 patients survived 10 years after mastectomy. (Two other patients of Fischel's survived 10 years after onset, but only 3 years after mastectomy.§ Five of Daland's 100 patients survived 10 years after onset, despite the absence of treatment by surgery, radium, or x-rays—a striking observation of Daland's.

Fischel's was the younger series of the two by almost seven years (Table 2). The age group most responsive to radical mastectomy was that from 45 to 54 years, where mastectomy added four and one-half years to the life span of patients



Survival periods after onset of tumor.

(Table 3). Least responsive was the group older than 60, where only three months was added to the span of life. Patients younger than 39 responded to mastectomy fairly well and had one year added to their span of life by treatment.

Fischel's youngest patient was 27 when she underwent radical mastectomy for carcinoma without axillary metastases, and after operation she married and bore two normal children; however, the 10th year metastases developed in bone, causing her death the 12th year, despite irradiation of bone. Fischel's next youngest patient

§ When comparing patients with Daland's, Fischel calculated survival times from onset of tumor, as Daland did; otherwise, Fischel's were postoperative times. Without tabulation, this was confusing. Fischel's survival times, calculated both after operation and after onset of tumor, are presented here.

Time, Yr.	Survivors After Operation	Survivors After Onset of Tumor
5	39	45
10	21	23
	A. No Axillary Metastases at Radical Mastectomy (28)	
5	18	20
10	11	12
	B. Axillary Metastases at Radical Mastectomy (72)	
5	21	25
10	10	11

was also 27, but hers was a cancer locally advanced in the breast at the time of radical mastectomy, and she died the third year after onset. Daland's youngest patient was 31 at onset and died the third year, untreated. Fischel's oldest was a patient of 76 who survived radical mastectomy and was clinically well the 14th year, despite ovariectomy in the 12th year for a second primary carcinoma of the ovary. Daland's oldest, aged 87, "died early" untreated.

TABLE 1.—*Survival Times After Onset, 1953*

	5 Yr.	10 Yr.	15 Yr.	20 Yr.
100 treated,* 1928-1944, Fischel	45	23	10	1
100 untreated, 1927, Daland	22	5	0	0

* See text footnote §, p. 821.

TABLE 2.—*Age, Sex, Race*

	Age at Onset, Yr.			Sex		
	Average	Youngest	Oldest	Female	Male	Race
Treated, Fischel	51	27	76	98	2	W
Untreated, Daland	57½	31	87	98	2	W

TABLE 3.—*Survival by Age, Fischel vs. Daland Series*

Age, Yr.	Survival, Yr.		No. of Patients	
	Treated	Untreated	Treated	Untreated
27-39	4¼	3¼	13	3
40-44	6	4¾	13	9
45-54	7½	3	39	29
55-59	6¼	2¼	10	14
60-87	4⅝	4½	25	45

TABLE 4.—*Motherhood and Survival*

	Mothers Before Onset		Childless Before Onset	
	Survival, Yr.	Patients	Survival, Yr.	Patients
Treated, Fischel	6½	55	6⅝	23
Untreated, Daland	3½	55	3½	38

Fischel's 76 Christians outlived by six months his 21 Jews, a difference in survival times too small to indicate lack of tissue resistance to breast cancer among Jews.

Treatment, not parturition, was the factor in Table 4 which prolonged life, and mothers treated survived only three months less than women who were childless when undergoing radical mastectomy. Similarly, mothers untreated survived as long as those untreated who were childless. Cancer during pregnancy or lactation was encountered neither by Fischel nor by Daland; Fischel's patient who bore children after mastectomy has been noted in the discussion of Table 3.

The average time after onset when Fischel performed radical mastectomy was 10 months; his earliest mastectomy was 2 days after onset; his latest, 10 years after onset. Daland's untreated patients delayed their first consultation for one and a half years after onset on the average.

How long did "early" radical mastectomy prolong life, as compared with "later" mastectomy? "Only by six months" was the answer, when early mastectomy meant operation within one month of onset and when later mastectomy meant operation from the second to the sixth month after onset; 27 early operations yielded six and a half years' survival time, whereas 28 later operations yielded Fischel's patients six years' survival time. The prognosis for individual patients, however, proved unpredictable. Fischel's earliest mastectomy was done two days after a patient discovered a breast tumor, and she survived 15 years; Fischel's next earliest mastectomy was done three days after a physician discovered a lump in the breast of the patient, who survived only 2 years.

"Very late" mastectomy, on the other hand, never prolonged life more than three years postoperatively for any of three patients upon whom Fischel operated "very late," i. e., from 7 to 10 years after onset. However, Vaughn || reported the 11-year postoperative survival of a Negro woman of 41 who had, at mastectomy, a tumor of 17 years' duration from the time of onset.

TABLE 5.—*Gross Staging at Mastectomy, Fischel Series*

Richards* Stage	Survival, Yr.	No. Patients	Tumor Size	Axilla	Skin Dimple	Nipple Retracted
1.....	7½	14	3 cm.	—	No	No
2.....	9½	14	6 cm.	—, +	No	No
3.....	5½	46	Any	—, +	Yes	Yes
4.....	3½	12	Any	—, +	Edema, ulcer, metastasis	
Total.....	6 yr. 1 mo.	100				

* McKinnon.[3]

For cancer "limited" to the breast (Stages 1, 2, and 3), mastectomy yielded two years' longer survival than for cancer "locally advanced" in the breast (Stage 4) to ulceration, skin metastasis of the breast, or extensive edema of breast skin (Table 5). Indeed, the 12 patients in Stage 4 in Fischel's series lived only one month longer after radical mastectomy than all 100 of Daland's untreated patients lived. Those larger, 6 cm. tumors of Stage 2 yielded two years' longer survival than those smaller, 3 cm. tumors of Stage 1, it was surprising to find. Skin dimpling or nipple retraction, signs some surgeons regard lightly, spelled two years' shorter survival for patients with these signs (Stage 3) than for patients lacking these signs (Stages 1 and 2).

Fischel's lone 5-year survivor when radical mastectomy was done for locally advanced cancer was a woman of 68 with a penetrating 4 cm. ulcer in the crease beneath the breast, fixed to fascia, with one metastasis in the skin above it and with hard nodes in the axilla; she survived mastectomy with skin graft for 14 years postoperatively. More typical, however, of Stage 4 was the death the second year postoperatively of a hospital nurse of 54 who reported with extensive *peau d'orange* about a 4 cm. central breast tumor with metastasis to the breast skin and hard nodes in the axilla. It should be noted that no patient underwent radical mastectomy in the presence of distant metastases clinically manifest at the time of operation.

|| Vaughn, A. N.: Personal communication to the authors.

Bleeding or discharging nipple occurred in four patients of Fischel's series and reduced their survival time to two and three-fourths years, indicating the seriousness of this symptom when it was accompanied by breast cancer.

How much did metastases shorten survival times? When the axilla was invaded at mastectomy, Fischel's 72 patients survived two and a half years less than when the axilla was not invaded, as in Fischel's remaining 28 patients (Table 6).

TABLE 6.—*Axillary Metastases and Survival, Treated Patients* *

Axilla at Operation	Postoperative Survival		
	Average	5-Year	10-Year
No metastases, 28 patients	8 yr.	18	11
Metastases, 72 patients	5½ yr.	21	10
Fischel's, 100 radicals	6 yr. 1 mo.	39	21

* See text footnote 5, p. 821.

TABLE 7.—*Postoperative Metastases and Survival*

Metastases	Treated, Fischel		Untreated, Daland	
	Average	Patients	Average	Patients
Bone	4¾ yr.	33	3¾ yr.	15
Liver	4¾ yr.	9	3¾ yr.	9
Subcutaneous	3¾ yr.	32	.....	..
Lung or pleura	3¾ yr.	9	2½ yr.	18

TABLE 8.—*Microscopic Grading, Fischel's Treated Patients*

A. Broders' Method*			B. Stewart's Method*		
Grade	Survival, Yr.	Patients	Infiltrating Carcinoma	Survival, Yr.	Patients
1	7	1	Papillary adenocarcinoma (and 2 Pagets)	7½	44
2	7¾	14	Lobular	6½	8
3	4½	31	Medullary	6	9
4	5¼	54	Sweat gland	6	1
			Comedo	5½	9
			Colloid	5	1
			Scirrhous	4	28

* Stewart.[5]

With bone metastases, mastectomy added one year to the life span of Fischel's patients as compared with Daland's (Table 7). Irradiation was credited as sharing with surgery the credit for this increase in longevity, for many of Fischel's 33 patients had irradiation of their bony metastases after surgery. With liver metastases, mastectomy also added one year to the life span of Fischel's patients. However, life was only one month longer for Fischel's 32 patients who postoperatively developed subcutaneous metastases than it was for all 100 of Daland's untreated patients. Nevertheless, all but seven of Fischel's patients were prevented, through treatment, from dying with ulcerative cancer" on their chests; how many of Daland's died thus, he failed to state. In passing, one noted that Fischel did grafts in only 17 of his 100 patients.

Did patients with differentiated carcinoma outlive patients with undifferentiated carcinoma after mastectomy? They did; and Fischel's 15 patients with differentiated carcinoma, Grades 1 and 2 (Broders') outlived by two and a half years Fischel's 85 patients with less differentiated carcinoma, of Grades 3 and 4 (Table 8). However, Fischel's tumors were difficult to grade because every tumor had cells of at least two of Broders' grades. When graded by Stewart's method, Fischel's 44 patients with papillary carcinoma outlived by three and a half years 28 patients with scirrhous carcinoma.

What ultimately became of Fischel's treated patients? Of his 100 patients, 3 died postoperatively, and 68 died of metastatic breast carcinoma by the 15th postoperative year. Here were, then, 71 patients whom radical mastectomy failed to cure of breast cancer. However, radical mastectomy definitely cured one patient who underwent operation at 61 and died the 14th year postoperatively free from metastatic breast carcinoma, her death being proved at necropsy to be due to a second primary carcinoma of the pancreas with peripancreatic, liver, and gall bladder metastases. Temporarily, radical mastectomy has "cured" 14 of Fischel's 100 patients, because they have survived clinically well to date, from 10 to 23 years postoperatively; eventually some will die of metastases. Fischel's remaining 14 patients, unfollowed from 2 to 15 years since operation, have been considered dead, because lost to follow-up.

Fischel refused radical surgery to 14 private patients during the period of 1928 to 1944 under study. His rate of operability was, therefore, 100 radical mastectomies for 114 patients, or 87%.

COMMENT

Rice has objected to comparing Fischel's with Daland's series because of differences in time, geographic location, and selection of patients; omission of inoperable patients from Fischel's series while including them in Daland's series, and differing ages. Certain of these objections were not answerable. However, comparable age groups gave the advantage to Fischel's over Daland's series. Even if Fischel's 14 inoperable patients were included with his operable patients, his survival time, though reduced thereby from six years one month to five years eight months, still exceeded Daland's survival time of three years five months. Furthermore, including Fischel's 14 inoperable patients with his 100 operable patients cut his 10-year survival rate from 21 to 19%, still yielding him a margin over Daland's rate of 5% survival at 10 years.

McKinnon believed the "curability" rate at 10 years for radical mastectomy would, if pathologists excluded borderline cancer, not exceed 10%. Fischel's rate at 10 years, when pathologists excluded borderline cancer, was 21%, and Fischel's rate at 10 years was 19% when his inoperable cases were included with his operable cases. Ten years, admittedly, was too soon to guarantee cure from breast cancer, however.

SUMMARY

Radical mastectomy usually prolonged the life of patients but failed, in the majority of them, to cure breast cancer. Although the prognosis for an individual patient proved unpredictable, nevertheless radical mastectomy significantly pro-

longed life when cancer had not spread, in the breast, to the stage of skin dimpling or of nipple retraction. Radical mastectomy proved incapable of prolonging life in groups of patients whose tumors had become locally advanced to the stage of ulceration, extensive skin edema, or skin metastases. However, the surgeon was advised still to perform radical mastectomy for "operable" breast cancer, pending proof of a better means of treatment.

The Chart was prepared by Philip A. Conrath.

DISCUSSION

DR. M. DAVID ORRAHOOD, St. Louis: I believe that any honest man who considers this problem of carcinoma of the breast must be willing to change his opinion on certain aspects of it. I know I have, and I am willing to change again.

One of the most interesting aspects of this study is that even after 10 years Dr. Keyes's patients continue to die. This tends to prove, to me, McKinnon's idea that if the Halsted operation is to cure cancer, it will do so only in the order of 8 to 10%.

If the Halsted operation does not cure cancer of the breast, then we must seek the reason.

From anatomical studies on carcinoma of the breast, we do not have to go very far to understand some of the reasons why the Halsted procedure fails. [Slide] In a recent study by the Pathology Department at St. Louis University, we found that of 50 patients on whom internal mammary node dissections were done, 11 showed metastasis to these nodes. In other series, such as the Handley and Urban series, the percentage of metastases in internal mammary and superclavicular nodes is greater than 60%. If the Halsted operation is to be successful, then it can be successful only in the 40% or less not showing metastases in either the internal mammary or the superclavicular nodes.

DR. WILLIS D. GATCH, Indianapolis: The following facts must govern any consideration of the effects of operation on the course of breast cancer.

1. Breast cancer kills not by its local growth but by its metastases, and the duration of life depends in great part on where these metastases happen to be.

2. To reckon the duration of the cancer (as is usually done) from the time the patient discovers the lump in her breast is plainly wrong. The cancer by then is already old. Its duration is from the time that it starts in a single cell or group of cells, and we know next to nothing about how long this is.

My colleague, Dr. Clyde Culbertson, was able to demonstrate cancers of minute size in a considerable number of breasts removed for lesions thought to be benign. The situation in the breast would seem to be the same as in the prostate. A pathologist at the Mayo Clinic found small cancers in 46% of the prostates of men over 50 who had had no symptoms of prostatic disease. Similar findings have been substantiated by five or six other pathologists, who have reported cancer of the prostate in from 16 to 36% of the cases they examined. Apparently, about 25% of all men over 50 have cancer of the prostate. I think it is obvious that most of these cancers of the prostate must undergo spontaneous cure; otherwise the incidence of death from cancer of the prostate would be tremendous. I believe that we are justified in the opinion that cancer undergoes spontaneous cure oftener than we have hitherto thought it does.

I believe tissue resistance is the main thing to consider in what happens to the victim of cancer, and we owe what good results we have, in great part, to this natural tissue resistance to cancer. A tissue resistance which is strong enough to hold cancer in check for 32 years or more, as has been repeatedly observed in cancer of the breast, may sometimes be strong enough to cure it.

3. Another consideration is that statements on the absence of cancerous lymph nodes in the axilla, based solely on the examination of the fresh specimen, are very unreliable. Specimens thought to be free of cancerous nodes on examination when fresh will often be found to have them when examined by a proper technique after they have been fixed in formaldehyde.

4. Our treatment, not only of cancer of the breast but of cancer everywhere, is founded largely on observations made by Halsted and Handley 50 years ago or more. They assumed that cancer of the breast spreads entirely, or nearly so, by way of lymphatics. I think that modern work, especially the work of Batson, shows that this position is untenable and that in all probability—and I haven't time to go into the evidence for this—cancer of the breast, and I think cancer in other organs, in many and possibly all cases, is also spread by way of the blood stream; so one is not going to cure it even if one does block dissection. Halsted and Handley taught that since cancer is a continuous growth, one can cure it by cutting all around it, through healthy tissue. One must be an optimist to believe that this is very often accomplished.

Our good results depend upon other things. In this respect it is interesting to note that Dr. Keyes brought out the point—and it takes temerity to make such an assertion—that results of early operation for cancer of the breast in many cases seem actually to be worse than operations performed later. The reason for that is (as some of the best students of cancer have brought out) that the more malignant growths grow faster, are recognized earlier, and kill earlier than cancers of the slower and less malignant types.

I think Dr. Keyes and his associates have made a praiseworthy effort to evaluate the worth of the Halsted operation. We need more observations on the natural course of cancer in the human being to guide our treatment and to help us evaluate its results. The authors have shown that the Halsted operation is of considerable benefit to the victims of breast cancer in most cases. They are right in their conclusion that we can never be certain that a cancer of the breast is cured in the pathologic sense.

Dr. Henry K. Ransom, Ann Arbor, Mich.: About three years ago we undertook a follow-up study of our cases of carcinoma of the breast which had been treated surgically, in an effort to determine if possible the value of prophylactic x-ray therapy. Patients operated on during the decade of 1935-1945 were selected for study. Thus, the minimum period for follow-up was five years, whereas some of the patients could have been followed for as long as 15 years. There were nearly 500 cases in the entire series. At the time of the follow-up, in 1950, it was found that approximately 70% were dead, and it was this group of 340 patients who were chosen for intensive study. In 285 cases radical mastectomy had been performed, and in 55 cases, simple mastectomy. These two groups are obviously not comparable. Contraindications to radical mastectomy were the usual ones, although our criteria were somewhat less rigid than those of Haagensen and Stout. Simple mastectomy was usually regarded as a palliative procedure for patients with distant metastases or with local disease so extensive that they were not acceptable for the radical procedure. It was hoped to avoid or eliminate ulceration and infection, and in most instances it was believed that the cancer removal was incomplete. Very rarely was simple mastectomy performed because of age or constitutional disease in patients with lesions suitable for radical removal. When the curves showing the percentage of patients dead at the end of from 1 to 15 years were plotted for the two groups, the two curves could be practically superimposed. Thus, at the end of five years 74% of the radical mastectomy patients and 78.8% of the simple mastectomy group were dead. At the end of 10 years 96.4% of the radical group and 96.2% of the simple group had died. The longest survival time in the radical group was 14 years, and in the simple group, 15 years (one patient in each). These data are of interest in view of Dr. Keyes report and show that patients with incompletely removed breast cancer may live not only 5, but occasionally 10 or 15, years. They, of course, should not be interpreted as indicating that radical mastectomy is no better than simple amputation of the breast. The answer lies in the fate of the 30% of patients who were living at the time of the follow-up. Only a small number of patients who had had simple mastectomy were living, usually with disease, and presumably the death rate curve would follow the same pattern as for the group already dead. In the radical group, on the other hand, were patients who had survived for 5, 10, or 15 years, who were free of disease, and for whom a clinical cure might be anticipated.

Dr. E. L. Keyes, St. Louis: In his 100 reported cases Daland found no spontaneous cure.

Dr. Gatch's observations on tissue resistance are very interesting. We know, for instance, that in the Jewish race carcinoma of the penis is almost unknown, and that in Mohammedans, who are circumcised at the seventh year, carcinoma of the penis occurs occasionally. We know

that carcinoma of the prostate is very rare in Jewish men, which is something we have been interested in at St. Louis University Medical School; there is something, therefore, in tissue resistance.

We still do radical mastectomies, I must say, for cancer of the breast, as the method of choice and shall until we are shown a better way.

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METASTATIC CHORIONEPITHELIOMA OF LUNG WITH NITROGEN MUSTARD THERAPY

Preliminary Report

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CHORIONEPITHELIOMA, which technically should be hailed by its correct pathological appellation of choriocarcinoma, is a rare tumor of fetal origin which is highly malignant and rather bizarre in its action.

According to Novak,[1] 50% follow in the wake of a previously existing hydatidiform mole; 25% arise from abortion, and 25% originate from full-term pregnancies. Ectopic gestation, as well as a few reported teratomata from various sites, has also been reported as an etiological factor.

A review of the literature, according to Mohler and McConnell,[2] reveals that approximately 2,000 cases have been reported. A statistical study by Novak [1] reveals an incidence of choriocarcinoma in the neighborhood of 1 in every 150,000 to 200,000 pregnancies.

Holman and Schurner,[3] in a review of 107 treated cases, noted the mortality to be 15% in those cases which were postmolar, and in those resulting from the stimulation of abortion and full-term pregnancies to be 40%. Hanley,[3] in reporting his findings in nine cases while discussing the above paper, reveals that his over-all mortality is 75%. A sprinkling of untreated cases which have been questionably diagnosed have undergone spontaneous regression.

The origin of this tumor has its inception in the fetal trophoblast which has obtained an unexplained stimulation causing the cells of the syncytium and Langhans' layer to change from their normal structure to a highly malignant one, using the maternal site (usually the uterus) as a host. Metastases by direct extension to vagina and by blood stream to the lungs and cerebrospinal system may ensue very rapidly.

Normal living chorionic tissue causes gonadotrophic stimulation, which is the basis of all positive animal hormonal tests for pregnancy. This stimulation in hydatid mole and more especially in choriocarcinoma becomes exceedingly marked and is found existent in high titers in these abnormal conditions of the trophoblast. This acts as an aid in diagnosis.

From the University of Nebraska College of Medicine.

Read at the Sixty-First Annual Meeting of the Western Surgical Association, Chicago, Dec. 5, 1953.

The treatment of uterine choriocarcinoma with metatases has been discouraging. In early recognition and treatment of the uterine tumor before metastases have arisen lies the hope in the cure of this neoplasm. Very often the suspicion of the attending physician is not aroused soon enough to make "an early diagnosis." Heller and Householder [4] report the development of choriocarcinoma of the uterus with pulmonary metastases following a full-term delivery in a 32-year-old patient and death on the 18th postpartum day from her disease, which was incidentally proved by autopsy.

All authorities agree that as soon as the diagnosis of tumor has been confirmed, the treatment of choice is immediate total hysterectomy. Most feel that the lutein cell ovarian tumors which may exist need not necessarily be removed, because they will regress with the removal of the primary tumor and suppression of hormonal stimulation produced by the neoplasm. With regard to deep roentgen therapy for pulmonary metastases, it is generally felt that the action is merely palliative and not curative.

The surgical approach for pulmonary metastases has been reported recently in two cases. Maier and Taylor,[5] in 1947, reported performing a lobectomy for metastases in the right lower lobe prior to doing a complete hysterectomy and bilateral salpingo-oophorectomy. Radiation to the lung fields followed surgery, and the patient had been well for three years at the time of writing. Kay and Reed [6] reported a right pneumonectomy for an apparent primary tumor in the lung in a 7-month-old girl.

The purpose in reporting our experience with one case is, first, to add one more case to the literature, since the disease is so uncommon that significant statistical data can be accumulated only by recording individual cases, and second, to annotate our handling of a case of metastatic pulmonary choriocarcinoma in which, fortunately, the patient at present is well and free from any further metastases.

REPORT OF A CASE

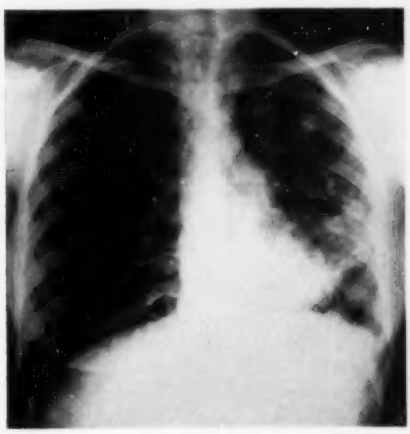
Mrs. M. B., age 25, primigravida and primipara, was seen by us on Sept. 2, 1952. She had recently been a patient in a tuberculosis sanatorium in another city and was being investigated for hemoptysis of several months' standing. After careful investigation at the sanatorium, she was found to have lesions in her left lung, and a series of x-ray films showed them becoming progressively larger (Fig. 1). She was found to be negative for tuberculosis and fungous infection, but spirochetes had been uncovered. Bronchoscopic examinations were negative on two occasions, and bronchogram with iodized oil (Lipiodol) revealed no evidence of bronchiectasis. Agglutination tests for Brucella were all negative. Her blood was normal except that the eosinophile count had risen to 7% at one time. She was given oxytetracycline (Terramycin) and penicillin as well as penthemate hydriodide (Neo-Penil) because of sustained hyperpyrexia.

This patient had delivered a normal boy on Feb. 28, 1951. This delivery was followed by a moderate lochia, which lasted eight days and culminated in a rather "heavy flow" which lasted until six weeks post partum. On her postpartum examination, her medical attendant dilated the cervix, and she stated the discharge ceased after this procedure. She stated that in August, 1951, she had "one extra period" and during the next three months had five periods. She also stated that a brownish discharge preceded her period two days and lasted approximately two days after the cessation of her periods. This continued until July, 1952, when she began to have a bloody vaginal discharge, which became almost continuous. At this time, a gynecological consultation was sought (18 months after the delivery of her normal pregnancy). Multiple punch biopsies of the cervix revealed no malignant lesion. Endometrial curettage showed no evidence of malignant change, but there was question of signs

of "decidual reaction." A Friedman test performed prior to the curettage was positive and remained positive subsequently with 0.5 cc. of urine. It was negative with the dilution to 0.05 cc. of urine. Pelvic examination showed no evidence of uterine enlargement or tenderness, and the adnexa were normal.

It was at this stage that the patient was first seen by one of us (H. E. A.), with a tentative diagnosis of chorionepithelioma of the uterus with metastases to the left lung. Examination showed a well-nourished woman troubled only with an occasional cough with slight hemoptysis. X-ray examination on Sept. 2, 1952 (Fig. 2), showed a marked infiltration throughout the entire left lung with some areas appearing rather discrete and somewhat rounded and other areas irregular in outline with fuzzy borders. The roentgenologists' impression was probable metastatic lesions of the left lung.

The pelvic examination under intravenous thiopental (Pentothal) sodium on Sept. 2 revealed the uterine corpus to be about normal size, shape, and position. The right ovary was palpable, with possibly a small hard mass about the size of a pecan just inferior to it; the left adnexa were negative; the cervix was normal, and the endometrial cavity was found to be 2 in. (5 cm.)



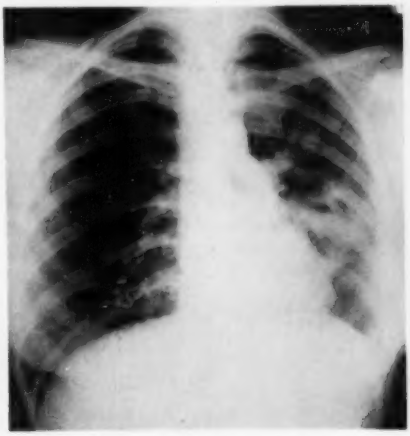


Fig. 1.—Hazy nodules in lower left lung area.
Fig. 2.—Increased infiltration noted throughout the left lung.

in length. Curettage produced a minimal amount of material. Small wart-like lesions from under the urethra and around the hymenal ring were removed for biopsy. The pathological report was (1) advanced secretory phase of endometrium with no evident tumor and (2) squamous-cell papilloma in the vaginal wall with chronic vaginitis. Papanicolaou slides of the sputum on Sept. 3 were negative for evidence of malignant growth. The Friedman test was positive in the dilution of 1 : 50.

On Sept. 3, intravenous pyelograms to rule out a teratoma of the kidney revealed a normal-appearing urinary tract. X-ray examination of the skull was negative.

On Sept. 5, a right salpingo-oophorectomy and total hysterectomy were done with a preoperative diagnosis of chorionepithelioma of the uterus. The uterus appeared to be about normal in size, shape, and position. The right ovary contained a small cyst, and the right tube appeared normal. The left ovary and tube also appeared normal. The pathological report was complete uterus with focal endometrial hemorrhage; ovary (right) with focal decidual reaction in serosa; Fallopian tube (right) without pathosis (Fig. 3).

Chest films on Sept. 12, 1952, showed mottled infiltration throughout the left lung, and the lesions appeared to be more discrete than in the previous films (Fig. 4).

A Papanicolaou stain of the sputum on Sept. 12, showed exudate of acute inflammation and hemorrhage with scattered atypical cells, possibly neoplastic. After consultation with an internist, thoracic surgeon, pathologist, and radiologist, it was decided, inasmuch as a definite diagnosis had not been made, that an exploratory thoracotomy should be done. Also, it was

Fig. 3.—Uterus and right tube and ovary which are essentially normal except for foci of decidual reaction on ovary.

Fig. 4.—Infiltration of left lung as noted in Figure 2, but more defined.

our opinion that if the lesions in the left lung were metastatic choriocarcinoma, they might be "solitary metastases," that is, metastases to a solitary organ and curable by resection. Furthermore, resection seemed justifiable in the face of the known tendency toward possible regression in other sites of metastases after removal of the primary one.

Consequently, on Sept. 20, 1952, a left total pneumonectomy was performed by one of us (J. D. B.) through an anterior thoracotomy incision. The lung was densely adherent to the chest wall, diaphragm, and mediastinal pleura in several places, and there were large hilar nodes which, removed for frozen section, proved to be inflammatory. Throughout the lung there were many firm masses (Fig. 5).

The pathological report by Dr. H. K. Giffen is most interesting. "Clinical diagnosis: Metastatic chorionepithelioma. Source of tissue: Left lung and lymph nodes. Gross: The specimen consists of six pieces of tissue. The largest piece is irregular, measuring 5 by 4 by 1.5 cm. It is firm and bluish-gray. The other pieces of tissue are much smaller and have the appearance of lymph nodes. Four representative sections are taken for microscopic study. Microscopic: Sections taken from the tumor masses in the lung show masses of poorly differentiated tumor cells showing pleomorphic arrangement, size, shape, and staining reaction. In some places there are syncytial masses with several nuclei; other areas show large cells with bizarre, irregular nuclei, and in many places large vesicular nuclei compose the solid sheets of tumor cells, with poor definition in cell borders, and sharply defined nuclear borders and large nucleoli. Necrosis and hemorrhage are marked and widespread. In many places there are central necrotic masses of hemorrhagic material in a ring of tumor. Mitoses are very numerous in most parts of the

Fig. 5.—Hemorrhagic multiple nodules throughout portions of left lung with tumor thrombi in pulmonary vein.

tissue. Many elements of subacute inflammation are shown, including large numbers of plasma cells, some leucocytes and lymphocytes. Fairly numerous eosinophiles are found in parts of the stroma. In many parts of the tumor there is blood in sinus-like spaces, surrounded by irregular masses of the tumor. Other areas in the lung around the tumor show again widespread edema and hemorrhage. No capsule is shown around the tumor masses. There are invasive tendencies widespread, and many vascular spaces are filled or partially filled with tumor. Other alveoli show masses of histiocytes filled with blood-pigment granules. Sections taken from lymph nodes at the hilus show marked reactive hyperplasia, with large secondary centers surrounded by hyperplastic lymphoid tissue, and marked reticuloendothelial hyperplasia. Most of the reticuloendothelial cells are phagocytic for blood cells and nuclear fragments, and large numbers show granules of blood pigment. No clear evidence of tumor invasion of the lymph nodes is demonstrated, however, but grossly and microscopically there is shown invasion of blood vessels, particularly veins. Diagnosis: Chorionepithelioma of lung (left), metastatic, with invasion into venous channels. Reactive hyperplasia in hilus lymph nodes (Figs. 6 and 7)."

The patient made an uneventful recovery from both the hysterectomy and the pneumonectomy.

She was dismissed from the hospital Oct. 2, feeling well, but the Friedman test was positive in a dilution of 1:50. At this time no metastases were demonstrable in the right lung in a postoperative film (Fig. 8).

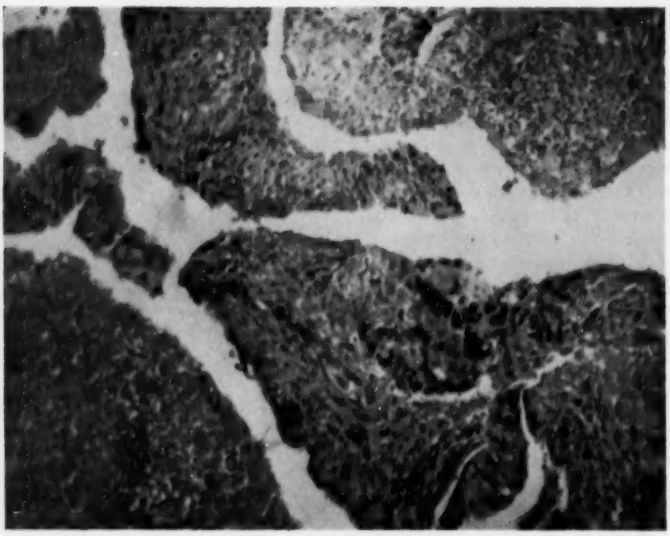


Fig. 6.—Part of tumor thrombus in main left pulmonary vein; × 105.

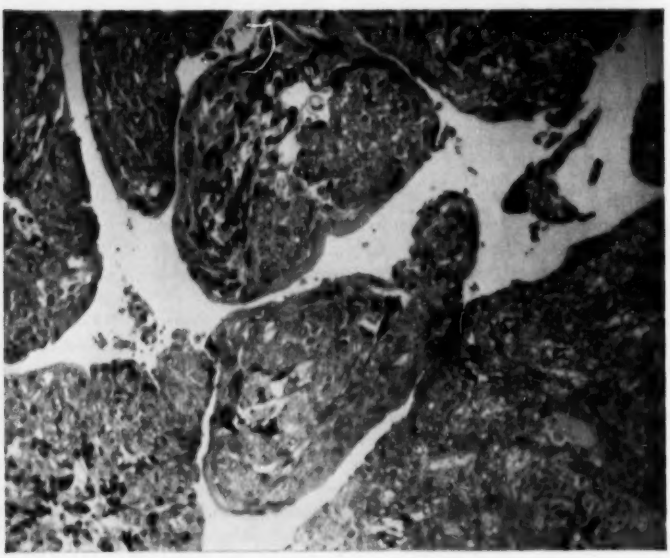


Fig. 7.—Pulmonary lesion chorionepithelioma in left lung.

After the patient returned home, she noticed a return of bloody sputum which had ceased after pneumonectomy. On Oct. 17, x-ray examination of the chest showed the following findings: "The entire left chest is opaque (4+). The heart and mediastinum are shifted toward the left. The right lung shows a mottling throughout the entire lung field and small, round, and characteristically metastatic lesions. There is no fluid in the angles. The mediastinum is clear. The apex is negative (Fig. 9)."

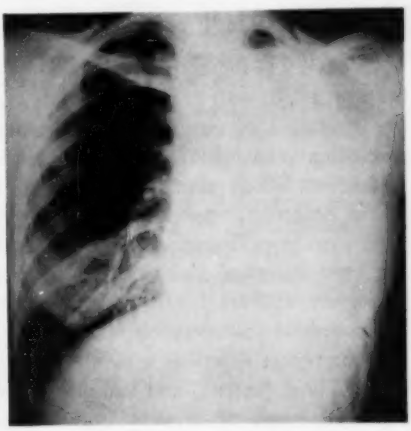


Fig. 8.—Left lung area obliterated due to pneumonectomy. Right lung shows no metastases.

Fig. 9.—In comparison with Figure 8, x-ray reproduction shows infiltration near base of right lung, supposedly metastatic.

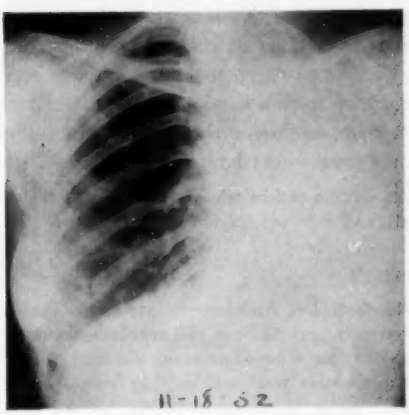


Fig. 10.—Regression of lesions of right lung.

Fig. 11.—Depicts complete regression of lesions of right lung, one year postoperatively.

With the apparent spread to the right lung, intravenous therapy with nitrogen mustard (methyl-bis[β-chlorethylamine] HCl) was instituted. Five injections of 5.7 mg. were given daily starting Oct. 17, 1952. The patient demanded to be released from the hospital.

She was readmitted to the hospital on Oct. 22, after ingesting 31 grains (2 gm.) of pentobarbital (Nembutal), with suicidal attempt, from which she recovered and returned home.

She was again readmitted to the hospital on Nov. 18, for further treatment with nitrogen mustard. At this time daily injections of 6 mg. were given intravenously for four days. On Dec. 3, the Friedman test was negative; also x-ray films of the right lung showed complete regression of the lesions as previously seen, and the lung appeared normal (Fig. 10).

Since her last hospitalization she has been feeling well and has had no further hemoptysis or other symptoms. Monthly Friedman tests have remained negative, as of this writing. A recent chest x-ray, which was taken one year postoperatively, is also negative (Fig. 11).

SUMMARY AND CONCLUSIONS

A review of the literature reveals that some 2,000 cases of choriocarcinoma have been reported, with varying mortality, ranging from 15 to 75%.

Treatment by complete hysterectomy has proved to be curative when choriocarcinoma is confined to the uterus and is indicated even in the presence of remote metastases. When pulmonary metastases have been encountered, deep x-ray therapy and androgenic hormones have been used, but the results in most instances have been merely palliative. A thoracic surgical approach for pulmonary involvement has been described in one patient who was living and well three years following lobectomy, and another in an infant that was subjected to a pneumonectomy with an immediate postoperative fatality.

Our report describes a case of choriocarcinoma which had presumably left the original host (uterus) and had metastasized to the left lung. Treatment consisted of right salpingo-oophorectomy, total hysterectomy, and left pneumonectomy, with a subsequent advancement of metastases to the right lung after pneumonectomy. To our knowledge, the use of nitrogen mustard therapy in the treatment of either primary or metastatic choriocarcinoma has not been previously reported.

From the dramatic response observed in our case, it would seem that further trial in the use of nitrogen mustard in the treatment of this bizarre fetal neoplasm is justified. It is quite probable that this tumor of fetal tissue is more sensitive than other types of tumor to a chemical poison such as nitrogen mustard. We are cognizant of the fact that no conclusions can be drawn from a single case and that there were several factors which may have been responsible for the regression of this tumor. One cannot escape the fact that spontaneous cures have been reported.

William S. Klein, M.D., of Spivak, Colo., cared for the patient while she was in the Sanatorium of the Jewish Consumptives' Relief Society and reported his findings to us.

DISCUSSION

Dr. J. Dewey Bisgard, Omaha: I prevailed upon Dr. Anderson to present this case. Even though it is a single case report and a premature report, there is still suggestive evidence (but only suggestive evidence) that nitrogen mustard might be effective in the treatment of this lesion, and it is going to be possible to evaluate this treatment only by stimulating a wide interest and obtaining experiences from many persons; consequently, we felt we were justified in presenting it on that basis.

It is possible that since a chorionepithelioma is a fetal type of tissue—in reality, a foreign tissue to the host—it might be more sensitive to a chemically toxic agent such as nitrogen mustard.

The question comes up, what was responsible for the regression of the tumor in this patient?

It seems to us that nitrogen mustard is the most likely possibility, because a dramatic change followed its use. Of course, we must be mindful that there are many examples of spontaneous regression.

Whether or not the hysterectomy had an influence, I do not know, but I am quite sure that the pneumonectomy contributed nothing and was, in retrospect, a useless procedure. However, we felt that possibly the pulmonary lesions represented solitary metastases, that is, metastases to a solitary organ, and knowing the tendency of such a tumor to regress when the major lesion or a primary lesion is disposed of, we felt that we were justified in doing a pneumonectomy.

Furthermore, we had not established the diagnosis beyond the biological tests; therefore, on that basis a total pneumonectomy might be justified. Again, this disease is interesting in that we have a biological test by which we not only can establish a diagnosis with reasonable certainty, but also can watch the progress of the disease, in this case the clinical change coinciding completely with the change in the Friedman test from positive to a negative and with the reappearance of the tumor, development of a positive Friedman reaction.

Dr. Harley E. Anderson, Omaha: I think that Dr. Dewey Bisgard had something to offer when he suggested that maybe—just maybe—nitrogen mustard had something to do with the seeming regression of this disease, because, inasmuch as this is fetal tissue, this toxic action may kill it more readily than maternal tissue.

There is one other thought that I believe we should consider. We do not see enough of these cases to draw very many definite conclusions, but Dr. A. T. Hertig was kind enough to look at these slides, and he compared them with a case in which the patient died on the 18th postpartum day; he felt that perhaps there was some difference in the type of cells. This patient who died on the 18th day showed much more malignant cells than those in our case.

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PRESENT CONCEPTS IN THE TREATMENT OF EMPYEMA IN CHILDREN

J. H. HERTZLER, M.D.
A. E. MILLER, M.D.
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WILLIAM M. TUTTLE, M.D.
DETROIT

THE UNRESTRICTED administration of the wide-spectrum antibiotics to inflammatory diseases of the upper and lower respiratory tract has effected a remarkable reduction in incidence of and mortality due to empyemata thoracis. The general impression that similar changes may have occurred in the predisposing etiological factors, clinical course of, and complications of empyema of the thorax prompted this review of the experience of the past few years in order to evaluate current concepts of therapy.

MATERIAL

The patients included in this study were limited to infants and children admitted to the Children's Hospital of Michigan from January, 1949, to July, 1953. It was felt that by limiting the study in this manner, rather than including our experience during this period at various other institutions, a more representative evaluation of relative incidence and indications for the various therapeutic measures would result. All the children in this study had collections of exudate in the pleural space definitely associated with, or secondary to, infection of the respiratory tract or pleural membranes.

INCIDENCE

Forty-one patients were hospitalized during this four and one-half year period in which empyemata thoracis was a primary or secondarily associated diagnosis. This is an average of approximately nine hospital admissions a year for this period. Previous studies made by Penberthy and Benson and reported in 1936 and 1941 revealed an average of 40.7 admissions annually for the period of 1926 to 1936,[1] and an average of 28 admissions annually for empyemata thoracis in 1936 through 1940.[2] Although Children's Hospital accepts patients up to and including 12 years of age, it is important to note that the youngest child admitted with this disease was 1 day old, the oldest 9 years, and the average age was 21 months. There was no significant difference in sex distribution, there being 17 girls and 24 boys reviewed.

Read at the Sixty-First Annual Meeting of the Western Surgical Association, Chicago, Dec. 5, 1953.

From the Department of Thoracic Surgery, Children's Hospital of Michigan, and the Department of Surgery, Wayne University College of Medicine.

ETIOLOGICAL FACTORS

Interest in a clinical review of empyema in children was stimulated in part by an unexpected increase in admissions for this disorder during the spring months of 1952. An analysis of etiologic factors in that group of patients revealed a remarkably similar history. The metropolitan area of Detroit had just weathered one of the largest measles epidemics in its history. The majority of the patients had had measles two to six weeks prior to admission. Their convalescence was not complete. They remained listless and lethargic for several days to weeks longer than normally expected, then abruptly became more severely ill than at any time before, with fever, cough, dyspnea, and chest pain, and were admitted with a diagnosis of empyema. This set of circumstances was the most common etiological history in 1952. The increased incidence in 1952 accounted for 35% of the total cases presented in this report.

Pneumonia with effusion remains the most frequent precursor to empyemata thoracis. Table 1 lists the primary or associated conditions so far as could be determined by history and clinical course.

TABLE 1.—*Etiological Factors*

	Patients, No.
Postpneumonic effusion	15
Measles (2-6 weeks prior)	10
U. R. I. or "chronic cold"	8
Septicemia or bacteremia	5
Bronchial pleural fistula and pyopneumothorax	2
Infantile eczema	1

THERAPY AND INDICATIONS

The primary objectives in the treatment of empyemata thoracis are (1) sterilization of the infected areas and (2) early obliteration of the pleural spaces. The therapeutic measures employed similarly have undergone little change except for the addition to the armamentarium of surgical and chemical decortication of the trapped lung.

For the purpose of analysis of therapeutic measures employed, those patients responding to specific antibiotics and aspiration therapy alone were classified as responding to medical means. When surgical intervention in the form of intercostal tube drainage, or decortication, or both were employed, the patients were classified as requiring surgical measures for eradication of the thoracic empyema. Eighteen, or 43%, of the empyemas required only medical therapy for satisfactory resolution. Twenty-three, or 57%, required surgical intervention. Of these 23 cases, 15 patients required intercostal tube drainage; 9 patients were treated by pulmonary decortication. Two patients had intercostal tube drainage but ultimately required decortication for satisfactory resolution. Seven were treated by primary decortication. Table 2 summarizes this statistical data.

The analysis of the duration of the illness showed an interesting relationship to type of therapy required. There is little question that the earlier specific measures are instituted which will obliterate the pleural space, the less often the more radical surgical procedures are required. Once the empyema is established every effort

should be made at the earliest time to evacuate the pleural space. The specific antibiotics often sterilize the pleural exudate, but they will not bring about its resolution once organization of exudate has commenced. This must be done by aspiration, drainage, or decortication. Often the clinical improvement resulting from decreased toxicity with the use of specific antibiotic therapy is presumed to indicate that satisfactory resolution is under way. This delay only permits time for organization to continue and the complications of empyema, bronchopleural fistula, fibrothorax with scoliosis, and entrapped lung to occur. Whenever pleural effusion appears in

TABLE 2.—*Statistical Data*

	Patients	
	No.	%
Medical (antibiotics and aspiration)	18	43
Surgery	23	57
Decortication (9)		
Tube drainage (15)		

TABLE 3.—*Length of Illness Prior to Specific Therapy*

	Illness Prior to Therapy, Days
Medical	5-30 (average 17)
Drainage	5-40 (average 14)
Decortication	14-90 (average 41)

TABLE 4.—*Indications for Tube Drainage*

	Patients, No.
Pyopneumothorax with fistula	6
Inadequate evacuation by aspiration	4
Reaccumulation of fluid	3
Dyspnea and toxicity	2

the presence of infection, every effort must be made to evacuate the pleural space at the earliest possible moment. Table 3 shows the relationship between the elapsed time from onset of illness and the initiation of specific therapy and the various procedures required for adequate resolution.

INDICATIONS FOR INTERCOSTAL TUBE DRAINAGE

Aspiration and drainage of the pleural space aid in the treatment of empyema by reducing the quantities of bacteria and their toxic products which the host must combat. Obliteration of the pleural space is equally important to prevent reactivation or reinfection and to prevent permanent damage to the efficiency of the underlying lung. Therefore the initial thoracentesis for diagnostic purposes should also be

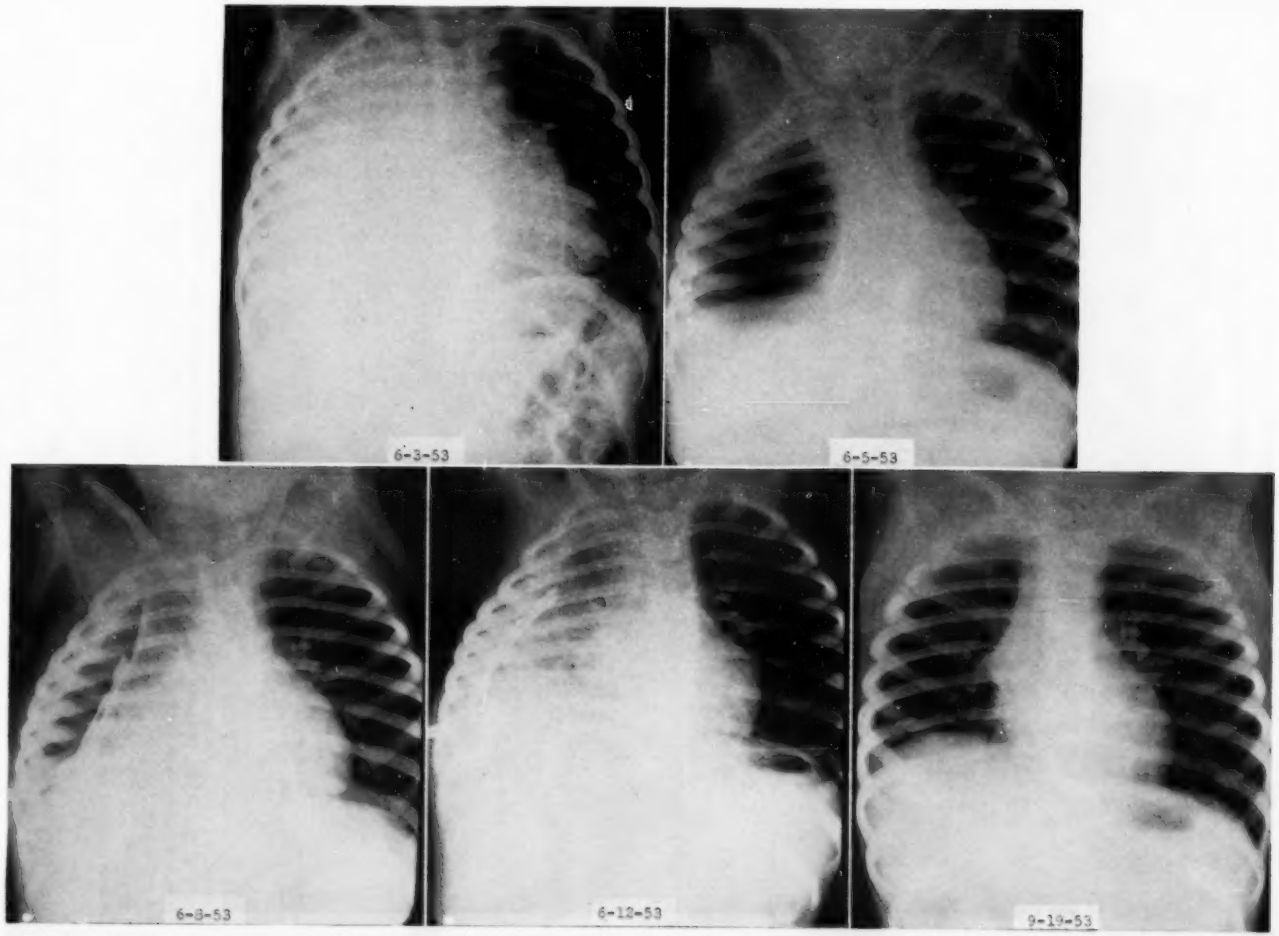

Fig. 1.—K. R. 3½-year-old white girl. This patient, admitted on June 3, 1953, had a massive right pleural effusion. The roentgenogram of the chest taken on June 5 reveals a tension pneumothorax which occurred after repeated attempts at aspiration. The roentgenograms taken on June 8 and 12 show the expansion following intercostal tube drainage.

the onset of specific therapy directed toward obliteration of the pleural space. If the initial attempts at aspiration do not adequately evacuate the space and there is no primary indication for decortication, tube drainage should be carried out immediately. Occasionally tube drainage of the pleural space is indicated even though

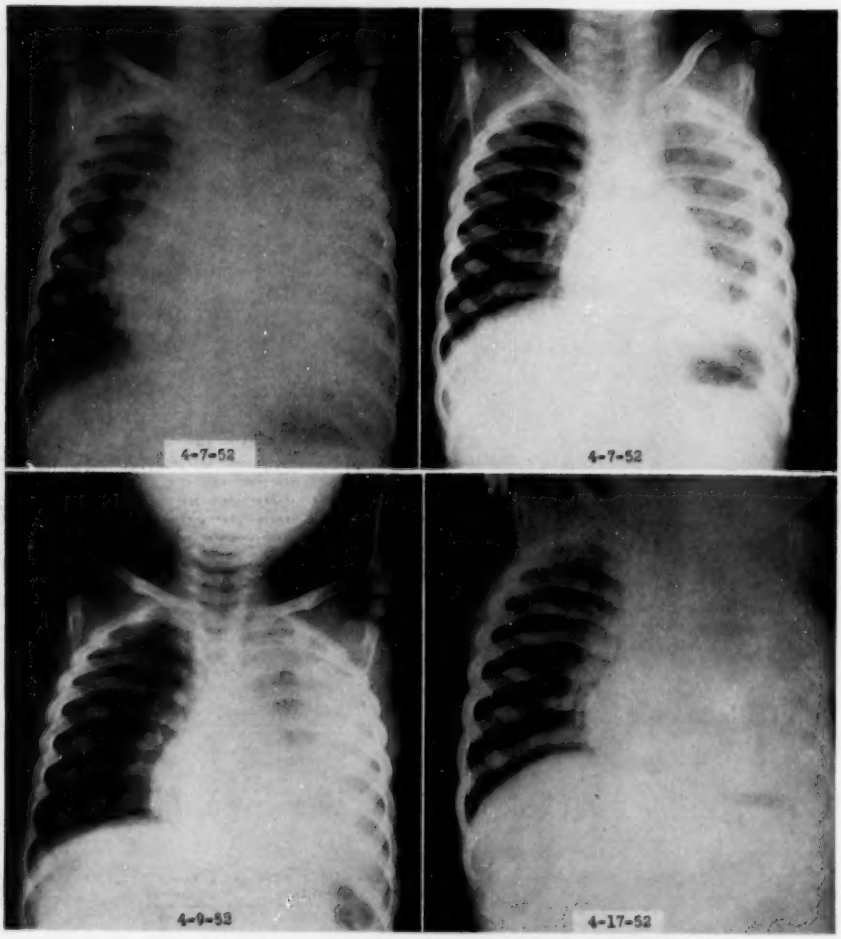

Fig. 2.—P. F., 18-month-old Negro girl. The roentgenograms of the chest reveal a massive effusion in the left pleural space. Aspiration of the left chest, later on the day of admission, April 7, 1952, resulted in marked clearing and almost complete reexpansion. The roentgenograms taken on April 9 and 17 revealed progressive reaccumulation despite repeated aspirations. The bacterial flora of this empyema was predominately a hemolytic Streptococcus.

decortication is anticipated in order to relieve dyspnea of pneumothorax (Fig. 1) or massive effusion, or to decrease toxicity by the evacuation of the pus within the pleural space. Table 4 lists the indications for intercostal tube drainage in those patients in whom it was employed.

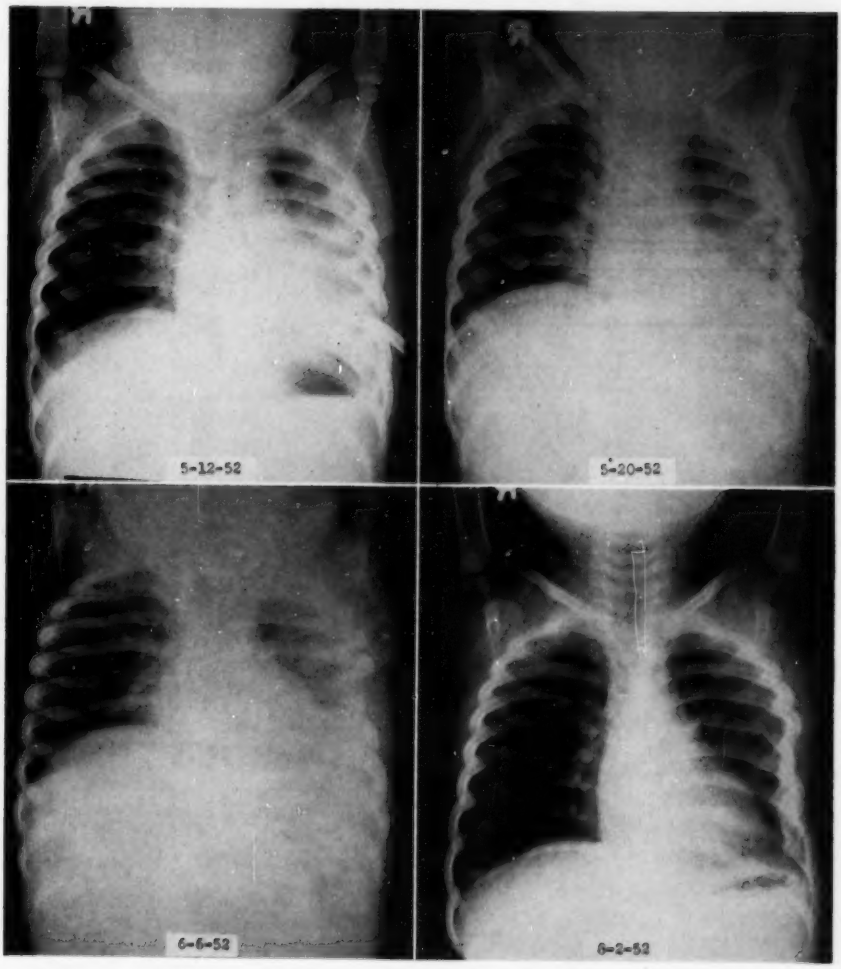

Fig. 3.—Same patient as in Figure 2. Closed-tube drainage of the pleural space was instituted. The chest roentgenograms taken on May 12 and 20, 1952, reveal that organization has progressed to a degree at which reexpansion was impossible. The chemical lysing agents were employed during this period, without significant benefit. The roentgenograms taken on June 6 and on Aug. 2 show the clearing and resolution accomplished after surgical decortication of the lung.

INDICATIONS FOR DECORTICATION

Decortication is a constructive reparative procedure directed toward evacuation of the organized material from the chest, closure of persistent fistulae if present, and freeing the encased lung so that it can reexpand to fill and obliterate the pleural "dead" space. A willingness to employ decortication early when specific indications

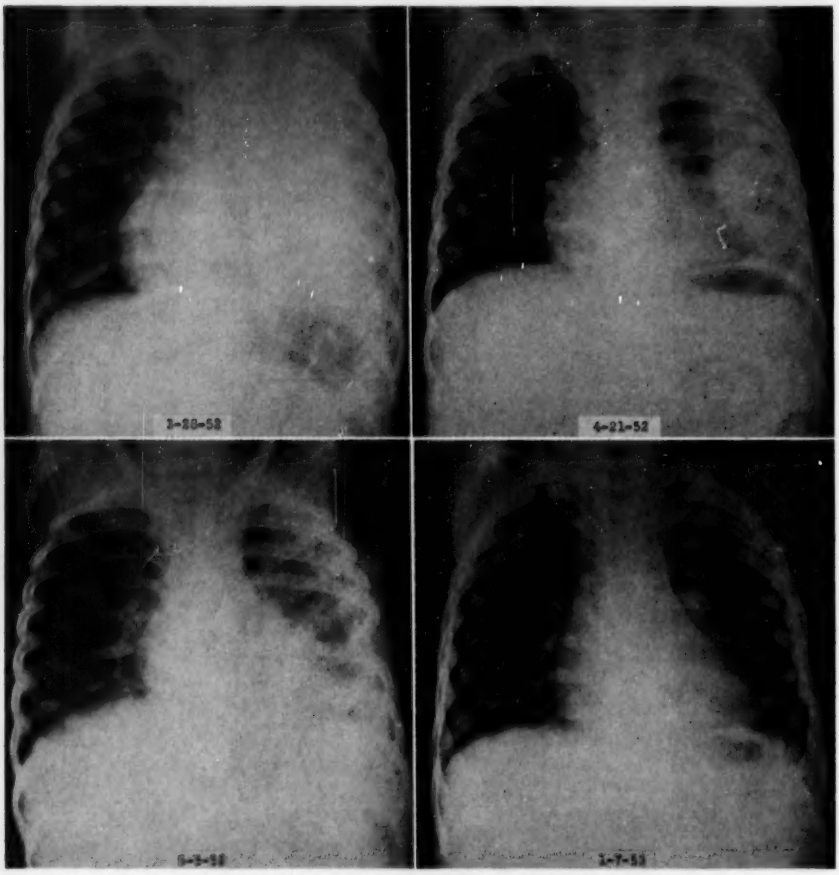

Fig. 4.—D. H., 3½-year-old Negro boy. The roentgenograms reveal the progress of this child after initial aspiration indicated that reexpansion of the lung and evacuation of the pleural space would not be accomplished. The chest roentgenogram taken on April 12, 1952, shows the typical appearance of the "trapped" lung. The roentgenograms taken on May 5, 1952, and on Jan. 7, 1953, reveal the postpulmonary decortication results.

are present, will materially decrease morbidity, avert development of complications secondary to chronic empyema, and restore a more functional respiratory system.

Primary indications for decortication are the trapped or encased lung which is held secure in the "peel" of organized exudate over the lung surface. Evidence of this situation is failure of the lung to expand despite adequate drainage, repeated aspirations (Figs. 2 and 3), or the inaspiratable empyema. Loculation of exudate

characterized by irregular collections of fluid and air within the chest requires decortication (Fig. 4). Persistent bronchopleural fistulae are best closed by decortication, thus enabling the lung and fistulous site to adhere to the chest wall and further insure closure. Table 5 reveals the indications for decortication in these patients. The underlying cause of each of these indications was the trapped lung.

TABLE 5.—*Indications for Decortication*

	Patients, No.
Reaccumulation of fluid	4
Chronic empyema	2
Unsuccessful aspiration (tube, etc.)	2
Loculated pyopneumothorax	1

TABLE 6.—*Bacteriological Flora Present with Various Types of Therapy*

	Patients, No.
Medically treated	
Sterile culture	8
Hemolytic Streptococcus	2
Hemolytic Staphylococcus	3
Diplococcus pneumoniae	2
Culture not made	1
Tube drainage	
Hemolytic Staphylococcus	6
Sterile on repeated culture	2
Hemophilus influenzae	2
Diplococcus pneumoniae	2
Bacillus pyocyaneus	1
Escherichia coli	1
Hemolytic Streptococcus	1
Decortication	
Sterile culture	4
Hemolytic Staphylococcus	3
Hemolytic Streptococcus	1
Diplococcus pneumoniae	1
Mortalities	
Hemolytic Staphylococcus	1
Hemolytic Str. and Staph	1

BACTERIOLOGY

Macauley [3] has pointed out that although the pneumococcus causes the great majority of pneumonias, there is a relative as well as an absolute increase in staphylococcal infections of the lung and pleura since the introduction of chemotherapy. Others * have pointed out the high incidence of staphylococcal infections of the respiratory tract with associated empyemas which require surgical intervention. In this series the sterilizing effect of antibiotic therapy given sporadically and indiscriminately prior to admission to the hospital is reflected in the larger numbers of sterile effusions which still require surgical intervention. It is necessary to point out the work of Langston and Tuttle and others which demonstrates that loculations occur in the pleural space which may be sterile, while other loculations still are

* References 4 and 5.

heavily contaminated with organisms. At least one such circumstance was encountered in this series. Repeated aspirations were sterile on culture and smear, but at decortication several areas were encountered which contained thick creamy pus loaded with staphylococci. This situation undoubtedly occurs more frequently than appreciated and accounts for instances of reactivation and chronicity in some patients. Table 6 reveals the bacteriological flora which were present with the various types of therapy employed.

The two deaths in this series occurred in newborns seen in 1949, both of whom died in the first few days of life. The empyema present was a complication of bacteremia or septicemia.

COMMENT

It may appear a bit trite to again bring up the subject of treatment in empyema of the thorax in view of the many papers which through long years have been written on this subject. However, we have felt justified because of the vast change which has occurred in its incidence, the increased numbers of complicated empyemas, and the change in bacterial flora.

It was demonstrated many years ago by Heuer [6] that the relative frequency of empyema in any given year was directly proportional to the virulence of the organism causing the pulmonary infection. Thus, in those years when the pneumonic process was mild and the death rate low, the incidence of empyema was also low. Empyema of the thorax is probably only rarely a primary disease.

The discovery of the various antimicrobial drugs greatly reduced the incidence, fatality, and morbidity of pneumonia. Although the complication of empyema became less frequent, it was recognized by Blades [7] and others that the incidence of the complicated empyema had increased. This was due primarily to the inaspiratable empyema and the loculated empyema. In the years 1938 to 1941, the incidence of the complicated empyema was 1% at the St. Louis Children's Hospital, and it rose to 5% after the introduction of the sulfonamides. This is not an indictment of such therapy. It is only a statement of fact which is of interest. It likewise is a challenge for new methods of surgical approach.

It is of interest to note that between the years 1926 and 1941, there were 551 children treated for empyema at the Children's Hospital of Michigan. Six cases, or 1.1%, were considered as complicated and became chronic in type. During the period of 1949 to 1953, there were seen 41 patients suffering from empyema. Nine of these, or 21.9%, required decortication to heal their disease. Before this operative approach the majority of such patients would have become respiratory cripples or would have died of chronic infection.

The change in the bacterial flora is of great import, for it has long been known that the Staphylococcus empyema was a difficult one to treat. The marked increase in this series of the Staphylococcus as the offending organism and of other less common types not encountered in the earlier series is of interest.

Chronic empyema in the child is a serious disease, for before the present pulmonary decortication it led to severe scoliosis due to fibrothorax or to the surgical procedures used to obliterate the chronic empyema cavity. Today, proper use of pulmonary decortication releases the captive lung to return to function. It restores the warped chest wall to its normal functional position. Its early use in those patients with captive lung or inaspiratable empyema is to be highly recommended.

SUMMARY

A report on 41 children with empyema of the thorax is presented.

Present-day concepts of treatment are described.

Newer complications and their management in an era of chemotherapy are discussed.

DISCUSSION

DR. LAWRENCE CHAFFIN, LOS ANGELES: We are grateful to Dr. Hertzler for bringing this subject to our attention again.

I think there are many here about my age who remember from medical school the discussion in Holt's textbook on pediatrics of empyema in babies and the fact that this disease was 100% fatal in babies under one year of age. About our time, the closed-catheter drainage of empyema was introduced.

I think one of my former chiefs, Dr. Wyman Whittemore, was one of the first persons to popularize this procedure, and with that the treatment of empyema in babies was greatly improved. Interest in it has greatly lessened with the advent of the antibiotics, and now, as Dr. Hertzler indicates, the subject has come to the fore again. I think it is a very timely and important presentation.

DR. CLIFFORD D. BENSON, Detroit: I just happened to have a part in the early phase of this treatment years ago, and I think that what Drs. Hertzler and Tuttle have brought out today is very important.

During the war we learned that this was a different phase of the empyema, simply because the patients were kept on chemotherapy, and when the aspirations were done on the medical service, the exudate and the pus was actually at the bottom of the pleural cavity. The supernatant fluid was amber-colored. Naturally, no pus cells were obtained high in the aspiration; therefore there was considerable delay before drainage was done. I think this group of cases brought out that one should not be satisfied with high aspirations. If one does a low aspiration, exudate and the pus cells will be obtained and then the indications for drainage are met much earlier.

DR. J. H. HERTZLER, Detroit: While we have been here, several men have approached us on this problem, because in their practices empyema is so extremely rare. They have questioned us about where and why we find these cases.

It has been shown by studies of pneumonia and empyema across the country, through the years, that certain localities and communities will have a peak year at the time another locality has a relatively benign year. There seems to be a definite cycling and relationship to the virulence and activity of the organisms. Certainly, today we are hearing much about resistant organisms, and we feel that this is playing a part in many of our complicated cases of empyema.

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TRAUMATIC CHYLOTHORAX

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TOPEKA, KAN.

A CASE of traumatic chylothorax is thought to be of sufficient interest to report and briefly discuss, inasmuch as it exemplifies some typical features of the disease and some of the factors which may cause a delay in diagnosis. The recent change in concept of treatment also justifies a brief review.

REPORT OF A CASE

A white man aged 34 years was injured in an automobile accident on June 25, 1951. He received fractures of the left 8th, 9th, and 10th ribs and the left transverse processes of the second and third lumbar vertebrae. He made satisfactory progress for seven days, when he suddenly became extremely short of breath, broke out in a cold clammy sweat, and complained of pain under the right costal margin. It was at this time that I first saw him. His pulse was rapid and weak, and his blood pressure was 90/60. His abdomen was not significantly abnormal, but the right chest was completely flat to percussion, with a total absence of breath sounds and a shift of the mediastinum to the left. With a presumptive diagnosis of hemothorax, a chest x-ray film was made, blood was matched for transfusion, and a thoracentesis performed. All who were present were amazed when 4,100 cc. of fluid was obtained, with dramatic relief of all his distressing symptoms long before the aspiration was completed. The fluid was tinged with pink but was basically of a milky color and clotted after standing. The similarity to chyle was mentioned, but since the fluid was on the right side and the thoracic duct was known to terminate on the left side, the possibility of a chylothorax was dismissed. The condition was assumed to be an infected hemothorax, and a specimen of the fluid was kept for future comparison. He was treated with transfusions, antibiotics, and general symptomatic measures.

No pus settled out from the fluid, and neither smear nor culture revealed any organisms. A review of the anatomy of the thoracic duct corrected the false assumption that this could not be a right-sided chylothorax, since the duct is actually on the right side through the lower half of the mediastinum.

There was some refilling in 48 hours, but he remained comfortable and did not require aspiration then. On the following day, however, he rapidly developed the same picture of collapse as three days previously, and thoracentesis returned another 3,500 cc. of the same sort of fluid. The laboratory confirmed the growing suspicion that the aspirated fluid was chyle.

During this interval a limited amount of reading had been done about chylothorax, and the picture was a most discouraging one. There were comparatively few cases reported; less than 50% had spontaneous healing of the ruptured duct; all had a rapid deterioration due to the loss of chyle, and nonoperative management had little to offer except postponement of the inevitable and continuous downhill course if the leak did not close spontaneously. The reports were suprisingly similar, advocating more or less the same general measures—repeated aspirations, sometimes replacing part of the fluid with air; intravenous infusion of at least part of the

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aspirated chyle, although it was admittedly the source of severe reactions which had even been fatal in some patients;* low-fat, high-protein diets, and supplementary blood, plasma, and general supporting measures. Most writers had no enthusiasm for operative intervention, describing it in extremely discouraging terms, such as "dangerous," [9] "a difficult surgical operation," [2] "not feasible" and "inaccessible technically," [7] "resulted in a mortality of 100%," [4] and "almost certainly lethal." [11] An exception, which was like a silver lining in the clouds, was Sweet's "Thoracic Surgery," [9] which sounded a more encouraging note and advocated a more active plan of treatment, saying that "the serious consequences of a continuing leak from the thoracic duct into the pleural cavity make it necessary to attempt to close the opening."

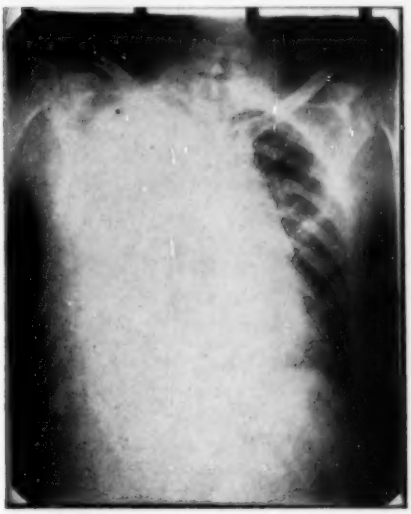

Fig. 1.—Roentgenogram taken before first thoracentesis.

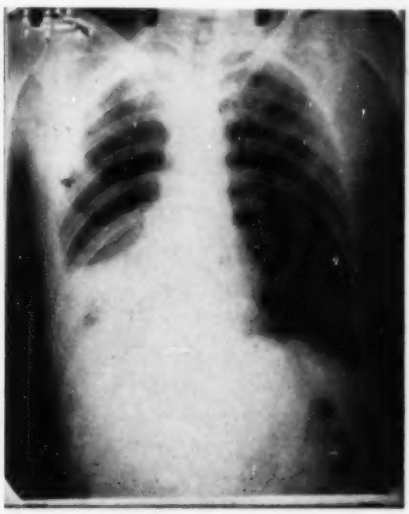

Fig. 2.—Roentgenogram taken immediately after first thoracentesis.

With this bit of encouragement and nothing encouraging about the nonoperative treatment, thoracotomy was recommended for ligation of the thoracic duct. At this time the patient had lost his appetite, was weak and listless, and the plasma protein level was down to 4.65 gm. per 100 cc.

In an attempt to increase his protein intake, Levin tube feedings were contemplated, but the patient remonstrated and promised that if I would "not put that tube down" he would eat anything we brought him. Surprisingly, he did eat his high-protein diet with supplementary protein feedings, but even that and transfusions did not prevent a small further decrease in his plasma proteins to a 4.5 gm. level the day before operation.

On July 10 (8 days after the first aspiration of chyle and 15 days after injury) a right thoracotomy was performed. When the pleura was opened, the chest appeared as if filled with cream. Although the fluid had not clotted in the chest, it did so soon after its removal. A small opening was evident in the mediastinal pleura a short distance above the diaphragm. As this was enlarged, dissection between the aorta and the azygos vein disclosed the open end of the lower segment of the thoracic duct from which clear fluid was running, and at a slightly higher

* References 14 and 19.

level, the open end of the upper segment. Both ends were ligated, and small segments excised for histological section proved it to be the thoracic duct. Presumably the fluid was clear instead of chylous because he had not had any food for 14 hours before operation. Another structure, thought to be the duct and cut before the actual duct was found, proved to be a small sympathetic nerve trunk. The proximity of the two structures and the ligation of sympathetic (splanchnic) nerves while searching for the thoracic duct have been described by others.[13] The mediastinal pleura was closed over the ligated duct and the thoracotomy wound closed with water-seal drainage.

His postoperative course was most gratifying. He ran a low-grade fever for a few days, but he began eating well—voluntarily this time—within 24 hours of the operation and said he felt better than before operation. He had only one more thoracentesis, that being on the 10th postoperative day, with recovery of only 150 cc. of serosanguineous fluid having no resemblance to chyle. He left the hospital on his 13th postoperative day, feeling well and with the plasma protein

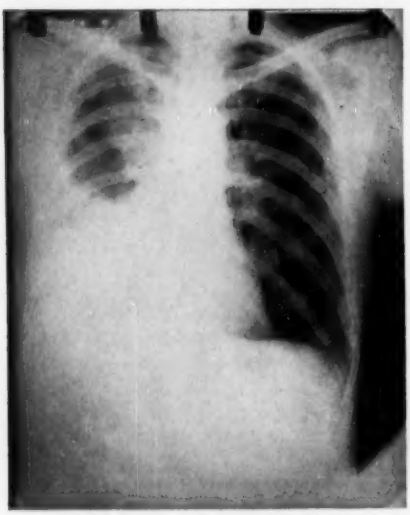

Fig. 3.—Roentgenogram taken one week after operation.

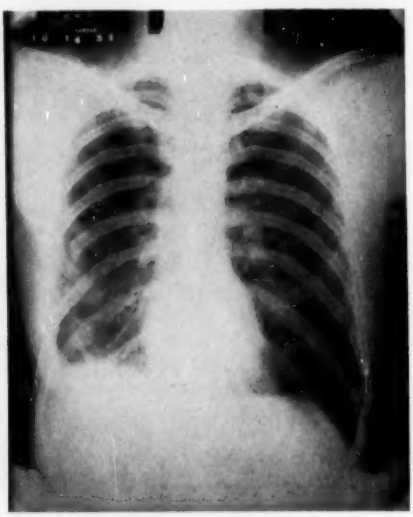

Fig. 4.—Roentgenogram taken three months after operation.

level up to 7.4 gm. per 100 cc. He continued to improve and has remained well since. A chest x-ray taken about three months later showed no accumulation of pleural fluid and a fully expanded lung.

Time does not permit a long discussion of traumatic chylothorax, and it would be superfluous, as excellent detailed accounts have already been written,† but a few facts are worth emphasis. There is characteristically a delay of three to eight days in the development of symptoms after injury, though it may be as long as several months. Symptoms are due to pressure or the loss of chyle or both. The pressure symptoms are those of any massive collection of fluid or air in a pleural space, while the continuous loss of chyle results in rapid emaciation and death, if not controlled. Chyle contains 60 to 70% of the fat absorbed in digestion and has from 3 to 6 gm. of protein in each 100 cc. Its content of nonprotein nitrogenous compounds, sugar, urea, and most minerals is similar to that of serum, and it will clot on standing

† References 1, 9, 10, 13, 15, and 16.

although not as rapidly as blood.‡ It is bacteriostatic, which accounts for the absence of complicating infection even after repeated thoracentesis.[10] It flows at a rate of 60 to 190 cc. an hour, and may exceed, 2,000 cc. in quantity in 24 hours. The loss of this amount of protein and minerals is obviously a serious threat to the welfare of a patient.

The diagnosis is commonly delayed or confused because of the latent period between injury and the onset of symptoms, the fact that the first tap is bloody, and the failure to think of the possibility of chylothorax.

About half the cases of chylothorax are traumatic in origin, the other half being associated with some fatal systemic disease.[13] The injuries reported to have caused chylothorax are quite varied and include crushing or penetrating injuries, falls, and hyperextension of the spine.[9] Chylothorax has also occurred as a complication of operative procedures involving the mediastinum or neck, especially in recent years as intrathoracic operations have become commoner. Among such procedures are esophageal resections, excision of a tumor of a right 10th rib, lumbothoracic sympathectomy, operation for tetralogy of Fallot, and left-sided radical neck dissections.§

Earlier cases were usually treated by some combination of the measures mentioned previously. In 45 to 50% healing was spontaneous, but the remainder were in a hospital for weeks or months, gradually declining and finally dying. Additional measures used in an attempt to decrease the accumulation of chyle include phrenicotomy, pneumothorax, thoracotomy for external drainage, thoracoplasty, various intrapleural injections and irrigations, and x-ray therapy, but these have not been successful with any constancy.[1]

Though ligation of the thoracic duct has been successfully done in the neck in cases of injury at that level,|| Lampson first demonstrated the feasibility of ligating it in the lower mediastinum, in 1946, reporting his case at the 1947 meeting of the American Association for Thoracic Surgery.[10] An additional case treated similarly was reported in 1948,[1] three more in 1949,¶ and two more in 1951.[16] There may have been other reports which I have been unable to find, but this makes seven cases of traumatic chylothorax treated by intrathoracic ligation of the thoracic duct since 1946. Six are reported as fully recovered, and the seventh was doing well six days after operation when reported in the discussion of another case.# This series, though small, makes a rather striking contrast to the reports of earlier series with a mortality of 45 to 50%.

I have been able to find only two reports of mortalities which are associated with ligation of the thoracic duct for traumatic chylothorax. Operated upon in 1942 and 1943, both patients died of an anaphylactic reaction during the intravenous administration of aspirated chyle.* These are not properly operative mortalities, but rather deaths resulting from a nonoperative therapeutic procedure now recognized as dangerous.

‡ References 9 and 12.

§ References 1, 3, 5, 6, 14, 16, 17, and 19.

|| References 11, 12, and Rumel, in discussion on Meade, Head, and Moen.[13]

¶ References 13, 20, and Klepser, in discussion on Meads, Head, and Moen.[13]

Klepser, in discussion on Meade, Head, and Moen.[13]

* References 14 and 19.

SUMMARY

Traumatic chylothorax is an uncommon condition which may result from a variety of injuries, including surgical operations involving the mediastinum or neck. Uncontrolled chylothorax produces a progressive nutritional deterioration leading to death. A brief period of nonoperative treatment is justified, hoping for spontaneous healing of the torn duct, but if there is not a significant decrease in the rate of accumulation of chyle, thoracotomy with ligation of the lacerated thoracic duct is at present the treatment of choice and can be expected to produce a good end-result. One additional case, so treated with recovery, is reported.

DISCUSSION

DR. DENTON A. COOLEY, Houston, Texas: I am surprised to learn how infrequently traumatic chylothorax is reported in the literature. Obviously the condition is much commoner than this review indicates. Chylothorax is a rare complication of thoracotomy for mediastinal lesions, and usually the leak in the thoracic duct seals off spontaneously without operation in several weeks. In the patient reported on by Dr. Clark, I wonder if the chylothorax may not have disappeared had he waited a little longer.

Recently, I was told of another method of dealing with chylothorax which I think is interesting. Dr. Eric Hardy, who is visiting us from England, describes a case in which the patient was cured within 24 hours of a persistent chylothorax of several weeks' duration. Dr. Hardy performed a phrenic crush on the same side as the effusion. The principle on which this form of treatment depends is that the sucking action of the diaphragm or the pleural space is reduced and the chylous fistula becomes sealed over and heals.

DR. EVERETT P. COLEMAN, Canton, Ill.: I have had no experience with chylothorax, but I have had one case of chylous ascites. A 10-year-old girl was struck in the abdomen by a baseball bat. Later on she developed a large amount of chylous ascites, which was aspirated on several occasions. We tried to find out what might be done to aid this condition but got very little advice and very little aid. Several tappings were done, and the condition finally cleared up. Then I realized we had a spontaneous cure.

A period of several months went by, and she began to reform fluid. Again we had more and more tappings, and finally we were drawing out about a gallon of fluid from this girl once a week.

The reason I want to mention this is that while she was somewhat subnormal mentally, she remained in a good state of nutrition. This seems almost unbelievable, but it is a fact. She had no malnutrition at all. She had a good appetite and was quite active physically, although quite poor in her studies in school.

We finally operated on her and found two possible sources of leakage, one at the junction of the duodenum and the jejunum. We simply made a little opening in the first portion of the jejunum and anastomosed it around the opening, and so far, she is apparently all right, but it is too soon to tell because she just left the hospital before I came to this meeting. It will take some time to determine whether or not she is cured.

There is an area above this where we opened into the lesser peritoneal cavity. We injected a dye called "sky blue" into the wall of the intestine below, and it did leak through the opening just described and did not seem to come from the opening above in the lesser peritoneal cavity. After some hesitancy, we left this alone.

There is a possibility that we may have further trouble. As I say, it is too soon to tell yet. The interesting thing to me was that when we were taking out a gallon a week, for several weeks, she did not show any malnutrition.

DR. ORVILLE R. CLARK, Topeka, Kan.: I did not want to create any impression that I thought there had been only seven cases treated. These were all I was able to find and to report. I am sure there must be many more which have been treated and have recovered, and no one has heard anything about them. If I were to do this again, I do not know that I would be so quick to operate, but at that moment it was so discouraging from the nonoperative point of view; intervention was about the only thing that looked encouraging, and operation seemed justified.

I think it might be perfectly proper and perhaps wiser to temporize a little longer and hope for spontaneous closure.

One point in technique that has been advocated as making it simpler to find the duct (which, had I known, would have helped at the time) is the matter of giving the patient some 4 to 6 oz. (120 to 180 cc.) of cream a few hours before operation, in order to have thick chyle coming out of the sinus at the time of operation.

One of the authors advocates giving one of the dyes at the same time in order to stain the chyle an outstanding color, such as green. I think that might make it a little easier to find the duct.

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SUBTOTAL ESOPHAGECTOMY FOR BLEEDING ESOPHAGEAL VARICES

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AND
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ALTHOUGH definite progress has been made in the management of patients with portal hypertension, control of hemorrhage from esophageal varices in such cases remains a challenge to the medical profession. Varices appear in the mucosa of the lower esophagus as evidence of portal hypertension in a significant percentage of such cases, whether the portal obstruction is intrahepatic or extrahepatic. Hemorrhage from the esophageal venous plexus may assume massive proportions, leading to fatal exsanguination, or result in repeated episodes of less severe bleeding, leading to chronic invalidism and secondary anemia. Esophageal varices are most frequently associated with portal cirrhosis. Eppinger [15] estimated that about 20% of patients with cirrhosis of the liver die of hemorrhage before ascites or hepatic insufficiency supervenes. Douglass and Snell [12] reviewed 444 cases of portal cirrhosis at the Mayo Clinic for the five-year period ending December, 1944, and reported that of the 85 patients who died, the cause of death was gastrointestinal hemorrhage in 49%. Similarly, other authors * have reported high incidences of massive bleeding as a cause of death in cirrhosis. Patek † reviewed 124 cases with Laennec's cirrhosis receiving modern medical treatment, and hematemesis occurred in 34%. Patients who had suffered one attack of hematemesis had a 50% chance of living one year. In the much less common condition known as Banti's syndrome, gastrointestinal hemorrhage is an even more frequent cause of death. Patients with Banti's syndrome tend to have repeated episodes of hemorrhage, usually of increasing magnitude, but life expectancy in the absence of liver involvement is relatively good.‡ The repeated bleeding, however, may lead to chronic invalidism and ultimate death from massive hemorrhage, cachexia, or intercurrent infection, even though the condition of the liver may be relatively normal up until the time of death. In the latter group of patients particularly it is evident that measures which would eliminate the bleeding would make the patient more comfortable and prolong life whether or not it would relieve the portal hypertension.

A number of methods for control of bleeding from the esophagogastric region have been proposed, and a few gratifying results have been reported with their use. These measures can be conveniently divided into the direct and the indirect approach.

Read at the Sixty-First Annual Meeting of the Western Surgical Association, Chicago, Dec. 5, 1953.

From the Department of Surgery, Baylor University College of Medicine, and the Jefferson Davis and Methodist Hospitals.

* References 18, 21 and 22. Patek, A. J. Jr., cited by Blakemore.[6]

† Cited by Blakemore.[6]

‡ References 21, 22, and 27.

The surgical treatment of bleeding esophageal varices and portal hypertension can be outlined as follows:

A. Indirect methods
   1. Measures designed to reduce volume of portal and coronary venous circulation
      (*a*) Splenectomy §
      (*b*) Ligation of splenic artery ‖
      (*c*) Ligation of splenic and short gastric arteries with splenectomy ¶
      (*d*) Ligation of left gastric and left and right gastroepiploic arteries #
   2. Measures designed to shunt blood from portal to systemic venous bed
      (*a*) Omentopexy [37]
      (*b*) Portacaval or splenorenal anastomosis *
      (*c*) Mediastinal packing †
   3. Measures designed to reduce intrahepatic venous obstruction
      (*a*) Ligation of hepatic, splenic, and left gastric arteries ‡
   4. Measures designed to reduce peptic ulceration of esophagus
      (*a*) Gastrectomy (subtotal and total) §
      (*b*) Vagotomy

B. Direct methods
   1. Measures designed to obliterate esophageal veins
      (*a*) Ligation of coronary veins ‖
      (*b*) Injection of esophageal varices with sclerosing solutions ¶
      (*c*) Gastroesophageal and esophageal tamponade #
      (*d*) Transesophageal suture *
   2. Measures designed to extirpate the esophagus and varices
      (*a*) Partial esophagogastrectomy †
      (*b*) Subtotal esophagectomy (Cooley and DeBakey)

Among the indirect methods are those which reduce the volume of the portal venous circulation, increase portosystemic venous communications, and reduce intrahepatic venous obstruction primarily by hepatic artery ligation, and, finally, those which reduce peptic ulceration of the terminal esophageal mucosa. The direct measures aim to eliminate the source of bleeding by obliteration of the varices or by their surgical extirpation. The various advantages and disadvantages of these have been previously considered. None has provided uniformly satisfactory results in the control of hemorrhage, and for this reason we should like to propose still another method that may offer a more effective approach to this difficult problem.

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‖ References 5 and 16.
¶ Banti, cited by Blakemore.[6]
# Flerow, cited by Spivack.[17]
* References 6, 7, 14, 20, and 35.
† References 19 and 32.
‡ References 4 and 25.
§ References 24 and 33.
‖ References 7, 23, and 35.
¶ References 9 and 23.
# References 28, 29, and 34.
* References 10, 11, 21, and 22. Boerema, I., cited by Linton.[21]
† References 24, 30, and 31.

Phemister and Humphreys [24] reported the first successful partial esophagogastric resection for bleeding esophageal varices, performed in December, 1946. This patient was a 21-year-old woman with Banti's syndrome, who had had repeated hemorrhages since childhood. Splenectomy had been performed at the age of 9, but hemorrhages recurred and became increasingly severe. Through a left thoracotomy approach, the left diaphragm was incised and the lower 3½ in. (8.8 cm.) of esophagus and upper 2 in. (5 cm.) of stomach were removed, and esophagogastrostomy was performed. A recent report [31] of this patient indicates that she is well and free of bleeding, four years later. Encouraged by this result and a few others,‡ we have modified the technique somewhat to include a more extensive subtotal esophagectomy, the purpose of which is to eradicate completely the entire segment of esophagus containing the varices. This is known to extend from the cardia to the level of the junction of the azygos vein with the vena cava, and occasionally a little higher. Moreover, we have used the combined upper abdominal, right anterior thoracic approach to the stomach and intrathoracic esophagus, for reasons somewhat similar to those previously indicated in the use of this approach for carcinoma of the esophagus.[13] Indeed, it is believed that this approach in cases with esophageal varices has certain additional advantages, namely, that it permits better exposure of the entire esophagus and, consequently, better control of hemorrhage during dissection with direct exposure of the azygos system, the preservation of which is particularly desirable.

The rationale of this procedure of extensive subtotal esophagectomy lies primarily in the complete and, it is hoped, permanent eradication of this source of hemorrhage. Admittedly, the operation may not influence the underlying condition which produced the esophageal venous collateral pathways, namely, portal hypertension. Indeed, some [24] have expressed concern over the possibility that interruption of these venous collateral communications may increase the portal hypertension and thus aggravate the condition. On the other hand, there are reasons to believe that transplantation of the stomach to this higher level provides opportunity for more direct drainage of portal blood into the azygos system. Moreover, by placing the esophagogastric anastomosis above the level of the azygos-vena cava junction, and consequently above the right atrium, the tendency for recurrence of esophageal varices is minimized. In addition to the more complete removal of involved esophagus, there may be some advantage in bringing the esophagogastric anastomosis well above the diaphragm to minimize the influence of the wide excursions in intrathoracic pressure upon the esophageal venous bed. These changes in pressure conceivably may have considerable influence by their milking action in promoting venous hemorrhage. In this connection, and on this basis, the use of temporary phrenic paralysis and pneumoperitoneum may have some value in the emergency control of hemorrhage. In these cases a further advantage of the more extensive subtotal esophagectomy and higher placement of the esophagogastrostomy lies in the reduced tendency for esophagitis to occur at this level, as has been previously noted.§ The causal relationship between erosive esophagitis and hemorrhage in esophageal varices has been well demonstrated clinically and experimentally.‖ For this reason,

‡ References 30 and 31.

§ References 13 and 37.

‖ References 2, 3, and 33

and because we believe that the esophageal varices constitute the primary and major source of hemorrhage, we doubt the necessity for removing a portion of the stomach. In light of these considerations the region of esophagus between the diaphragm and azygos-vena cava junction may be regarded as the critical zone for esophagogastrostomy in the presence of portal hypertension (Fig. 1).

TECHNIQUE

The procedure of subtotal esophagectomy which is employed for this purpose (Fig. 2) is somewhat similar to that described elsewhere for the treatment of carcinoma of the esophagus.[13] Only a brief description will be given here to direct

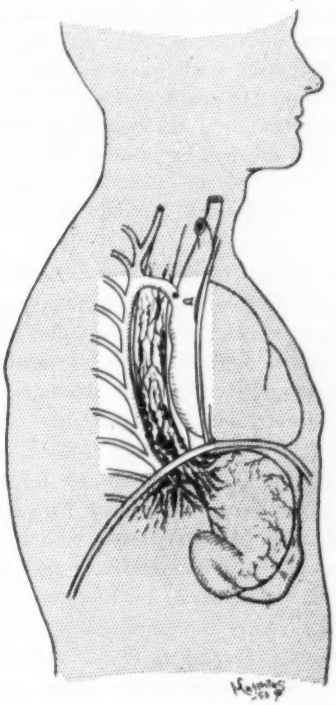

Fig. 1.—Drawing showing critical zone of esophagus, represented by unshaded area and extending from the level of the azygos-vena cava junction (*a*) to the diaphragm.

attention to certain modifications adapted to the treatment of esophageal varices. Patients are prepared for operation by correction of anemia with whole blood transfusions. Vitamin K injections should be given if there is evidence of reduced prothrombin activity. Esophagoscopy may be performed to determine the proximal extent of the varices but is usually not necessary.

The patient lies supine on the operating table with a small pad under the right shoulder and hip to elevate this side slightly, and the right hand and arm are suspended by adhesive strips from an overhead standard. With the table in the horizontal position, exploratory laparotomy is performed first. The incision is made

through the upper midline, but if a previous upper abdominal operation has been done, the same incisions may be employed again. Exploration of the peritoneal cavity is performed primarily to ascertain the presence of liver damage and to obtain a specimen of liver for biopsy. Pressure may be recorded in the portal venous bed for possible future reference. If the spleen has not been removed previously, and particularly if there is splenic engorgement or evidence of hypersplenism, then splenectomy is indicated (Case 1). Careful attention must be given to the dissection in the subphrenic space and in the retroperitoneal tissues because of the probable presence of an extensive network of thin-walled, dilated veins, the injury of which may lead to uncontrollable hemorrhage.

After splenectomy is completed, mobilization of the stomach is commenced for transplantation into the thorax. Beginning on the greater curvature of the stomach, the left gastroepiploic vessels are divided, preserving the gastroepiploic arcade. On the lesser curvature of the stomach the left gastric artery and vein are divided close to the celiac axis. The abdominal portion of the esophagus and cardia is exposed by incising the peritoneal reflexion at the esophageal hiatus. Phrenic vessels and vagus nerves are ligated and divided. Ordinarily, this mobilization is sufficient to allow the stomach to be drawn into the apex of the right pleural cavity, and the blood supply is adequately maintained through the preserved right gastric and gastroepiploic vessels.

Pyloromyotomy of the Fredet-Ramstedt type is routinely done in order to prevent troublesome gastric retention, which may occur in the completely vagotomized stomach. Only the serous and muscularis layers are divided over a distance of about 4 cm. proximal to the duodenum and pyloric vein, permitting the underlying mucosa to bulge into the pyloromyotomy incision. The abdominal incision is covered with a warm moist pack, and the retractors are removed.

The table is rotated to the left about 35 degrees and a curved right submammary incision is made (Fig. 2, inset). The chest is entered through the fourth intercostal space, the fourth costal cartilage being divided near the sternum. The margins of the incision are protected with moist packs, separated with a rib-spreader. By means of carefully placed moist packs and curved retractors the lung is displaced forward, giving adequate exposure of the posterior mediastinum. The posterior mediastinal pleura is opened longitudinally over the esophagus from the superior mediastinum to the level of the diaphragm. Although in two of our cases the azygos vein was divided, it is probably desirable to preserve this vessel, through which a large collateral venous bed empties into the superior vena cava.

The enlarged veins on the surface of the esophagus are divided close to it and ligated or sutured. The esophagus is encircled with gutta-percha drains for traction to facilitate exposure and division of the vessels on its posterior and left lateral aspects. When the esophagus has been mobilized, the stomach is drawn into the chest through the esophageal hiatus. This maneuver is simplified by inserting the right hand into the abdominal incision and the left hand into the thoracotomy incision. The hiatus can thus be stretched bimanually to about four times its usual size. By making traction on the esophagus above the diaphragm and threading the stomach into the hiatus below, one can deliver the stomach into the thorax without torsion. The stomach need not be sutured to the margins of the hiatus. After the stomach has been drawn into the thorax, the cardiac end of the esophagus is divided

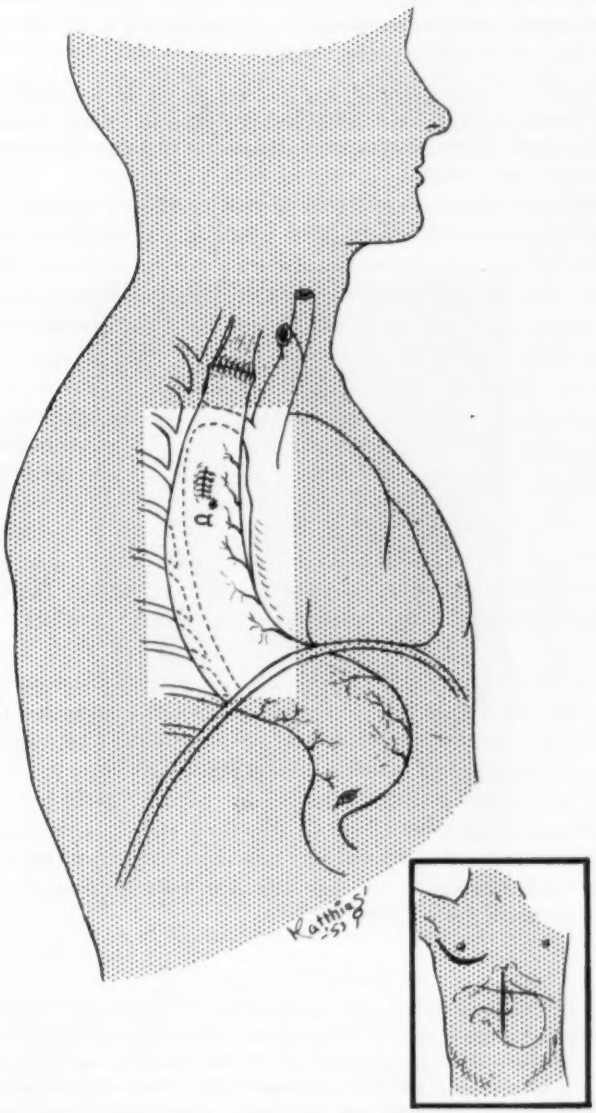

Fig. 2.—Drawing showing technique of subtotal esophagectomy for bleeding esophageal varices. The esophagogastric anastomosis is placed above the critical zone using the fundus of the stomach and closing the cardia (*a*). In the inset is shown the position of the laparotomy and right thoracotomy incisions.

between clamps. The distal stump is closed in layers by inversion, using a continuous fine absorbable surgical (gut) suture U. S. P. for the mucosal layer and an interrupted fine nonabsorbable surgical (silk) suture U. S. P. for the serosal layer. The proximal esophageal stump is temporarily occluded with a heavy silk purse-string suture, which is tied snugly to prevent leakage.

The stomach is drawn posterior to the hilus of the lung and into the upper thorax. Traction is made on the esophagus above the level of the azygos vein, and the distal two-thirds of the esophagus is drawn out of the superior mediastinum, leaving the azygos vein intact.

Moist packs and curved retractors are applied to the lung in order to compress the apex and allow exposure of the superior mediastinum. The lower portion of the right lung can be continuously ventilated during the remainder of the operation. In all instances the esophagogastric anastomosis is done more than 2 cm. above the level of the azygos vein and in some cases at the apex of the mediastinum.

The anastomosis is performed between the upper esophageal segment and a site on the anterior surface of the fundus of the stomach. It is done entirely with interrupted sutures of fine silk. The circumference of the anastomosis may be enlarged if necessary by splitting the esophagus 2 or 3 cm. in a longitudinal direction. A nasogastric tube is threaded into the stomach and suction is applied. The stomach is anchored in the upper thorax by multiple sutures to the mediastinum and parietal pleura in order to prevent traction on the line of anastomosis when the patient resumes an upright position. Through an intercostal stab wound a small polyethylene catheter is inserted into the pleural space for water-seal drainage. The thoracotomy and laparotomy incisions may then be closed simultaneously, to reduce the operative time.

In the postoperative period careful attention must be given to possible hemorrhage continuing from the moderately traumatized gastric mucosa and the need for blood transfusions to counteract blood loss. Precautions must be taken to prevent regurgitation and aspiration of gastric contents. This complication may be prevented by the use of intermittent gastric suction and by maintaining the bed in the semi-Fowler position after operation. Usually by the third or fourth day the nasogastric tube may be withdrawn and liquid diet may be started. When evidence of peristalsis returns, a soft diet is resumed, although attention must be given to the possible occurrence of excessive gastric retention.

REPORT OF CASES

Case 1.—R. P., 11-year-old white girl, was admitted to the Jefferson Davis Hospital on Jan. 29, 1953. Her initial illness began in January, 1952, with acute onset of fatigue, listlessness, anorexia, and progressive abdominal enlargement. Shortly thereafter she developed jaundice, hepatomegaly, and splenomegaly, but she was never febrile. The icterus subsided during the next two months, and she was well until July, 1952, when she developed gastrointestinal bleeding, manifested by hematemesis and melena. The abdominal enlargement returned and was associated with mild anasarca with puffiness of the eyelids. She was admitted to the Jefferson Davis Hospital on July 31, 1952, for observation. Laboratory studies revealed a secondary anemia (red blood cell count, 3,280,000; hemoglobin, 9.2 gm. per 100 cc.) and evidence of severe liver damage (serum bilirubin, 2.2 mg. per 100 cc.; total serum proteins 5.9 gm. per 100 cc.; albumin, 2.2 gm. per 100 cc.; globulin, 3.9 gm. per 100 cc.; sulfobromophthalein, 37% retention; thymol turbidity, 31 units, and prothrombin activity, 25% of normal).

A barium esophagogram revealed the presence of esophageal varices in the distal third of the esophagus. While in the hospital, she showed some improvement clinically; and the ascites subsided. She was discharged on Aug. 23.

During the interval prior to the present admission, she experienced four episodes of upper gastrointestinal bleeding with copious "coffee-grounds" vomitus and tarry stools, requiring hospitalization and blood transfusions in local hospitals. About two weeks before this admission she developed fever (104 F.) and shaking chills and again began to vomit blood and pass tarry stools. The fever subsided gradually under penicillin treatment administered by her local physician, but because of her poor general condition she was admitted to the hospital for further evaluation.

Physical examination revealed an acutely and chronically ill child with a temperature of 102 F., pulse of 132 per minute, and blood pressure 108/78 mm. Hg. The sclerae were icteric,

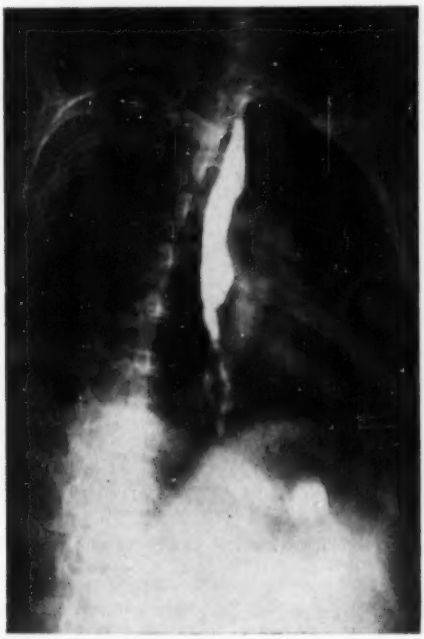

Fig. 3.—Roentgenogram of the chest and barium-filled esophagus in Case 1 demonstrating extensive esophageal varices.

and there was puffiness around the eyes. There were numerous spider angiomata over the neck and trunk. There was a prominent venous pattern in the skin of the abdomen, and there was moderate ascites. The liver was not palpable, but the spleen was enlarged 4 fingerbreadths below the costal margins. Rectal examination was negative.

Laboratory examinations revealed hemoglobin 10.5 gm. per 100 cc., red blood cell count 3,200,000 per cubic millimeter, leucocyte count 18,450 per cubic millimeter, segmented neutrophiles 73%, stab cells 10%, and lymphocytes 16%. The urine was dark yellow, contained no bile or urobilinogen, and was otherwise normal. Stools were strongly positive for blood. Blood chemistry determinations revealed a total serum protein of 5.3 gm., albumin 2.5 gm., and globulin 2.8 gm., per 100 cc.; thymol turbidity 22 units; prothrombin time 38% of control, and serum bilirubin 2.1 mg. per 100 cc. A blood culture was negative, and the Paul-Bunnell test (heterophile antibody) was positive in a dilution of 1:448.

Roentgenographic studies of the esophagus with barium revealed increase in the number and the size of esophageal varices (Fig. 3).

During the following month in the hospital she improved gradually on antibiotic treatment and multiple blood transfusions. The fever subsided gradually, but there was mild persistent gastrointestinal bleeding. In spite of the marked impairment of liver function, the decision was made to attempt to control the bleeding esophageal varices by extirpation of the esophagus.

On March 2, exploratory laparotomy was performed through an upper midline incision. The liver was strikingly contracted, fibrotic, and nodular, some of the nodules being 4 cm. in diameter. The spleen was enlarged, firm, and bright red. In the posterior peritoneal recesses there was an extensive network of vessels, which were hemangiomatous in appearance and contained bright-red blood. The portal vein was small and surrounded by angiomatous vessels, which extended up on the stomach and cardia. Pressure in an omental vein was 45 cm. of saline. The spleen was removed, and numerous vascular adhesions to the diaphragm were divided. After this, the proximal two-thirds of the stomach was mobilized for its ultimate displacement into the chest, and a pyloromyotomy was done. A right anterior thoracotomy incision was made

Fig. 4.—Photograph of resected specimen of esophagus in Case 1 showing multiple, superficial, dilated vessels in submucosa.

through the fourth intercostal space and the lung was retracted forward. The posterior mediastinal pleura was also involved with the angiomatous vessels found in the peritoneum, and the dissection was tedious, due to the continuous oozing from these vessels. After the esophagus was mobilized from its bed, bleeding was controlled by suture and ligature. The azygos vein was divided, and an esophageal gastric anastomosis was performed in the superior mediastinum. The operation required 4 hours 50 minutes, and during this time 2,000 cc. of transfused whole blood was given.

For the first 24 hours after operation there was persistent slow bleeding from both the indwelling gastric tube and the intrapleural water-sealed drain, and continuous slow blood transfusions were employed. The gastrointestinal hemorrhage subsided, but a hemothorax developed on the right side, which was treated by repeated thoracenteses. Improvement during the first week after operation was gradual, and she began to take a soft diet. She remained somewhat lethargic and had a persistent fever, the temperature ranging from 100 to 102 F. Attempts to evacuate the hemothorax were largely unsuccessful, and on the 14th postoperative day there was profuse drainage from the thoracotomy incision, after which the fever subsided. Because of the persistence of the hemothorax, evacuation of the hemothorax under ether anesthesia was performed on March 18. About 800 cc. of clotted blood was removed from the right

lower chest and a water-seal drain was inserted. No attempt was made to decorticate the lung completely. She became progressively more lethargic during the next few days and finally died in a coma on March 22, 1953.

Pathologic Report.—The spleen revealed gross and histologic changes indicating chronic congestive splenomegaly of Banti's syndrome. The resected esophagus was 9 cm. long, and there were small, rather superficial, collapsed longitudinal vessels which were visible through the mucosa (Fig. 4). Liver biopsy revealed distortion of the pattern of liver cells, with several large lobules of regeneration having interwoven cords of liver cells surrounded by distended sinusoids. Around the lobules there was proliferation of fibrous connective tissue and regenerated bile ducts. The appearance suggested posthepatic cirrhosis or chronic hepatitis.

Autopsy Findings.—The lower portion of the right pleural space was obliterated by an organized hemothorax. The esophageal-gastric anastomosis was intact except for a 2 mm. defect in the circumference, which showed no evidence of leakage. The liver was small, weighing 549 gm., scarred and contracted, with multiple large nodules of regeneration, and the cut surface revealed no areas of normal hepatic tissue.

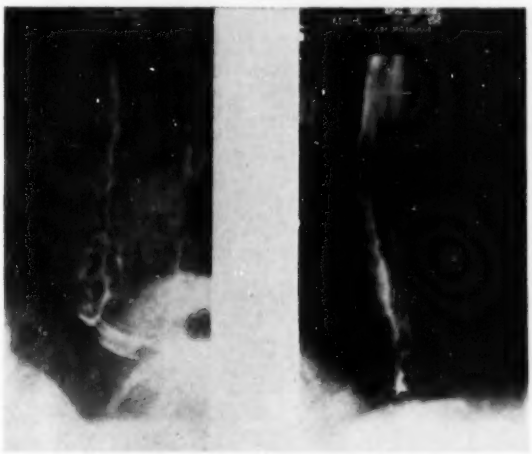

Fig. 5.—Esophagogram in Case 2 demonstrating extensive large varices throughout distal half of esophagus.

Case 2.—E. L., 35-year-old white married woman, was admitted to the Methodist Hospital on March 3, 1953, with a complaint of repeated hematemesis. Transient gastrointestinal bleeding with hematemesis first occurred in April 1950. A diagnosis of esophageal varices was made when severer hematemesis occurred in November, 1951, and again in February, 1952. Both these latter attacks required multiple blood transfusions. Hematemesis recurred in March, 1952, and 3,500 cc. of blood was administered. Splenectomy was done at this time by her local physician, who reported that numerous perisplenic adhesions, containing dilated veins, made the procedure difficult.

Following the splenectomy she remained well, with only occasional tarry stools, from March, 1952, to January, 1953, when a massive hematemesis occurred. From then until the present admission the patient had repeated hemorrhages, and, in spite of numerous transfusions, the hemoglobin had never been above 8 gm. per 100 cc. For the few months immediately preceding the present admission she was virtually bedridden.

Physical examination revealed a well-developed woman who appeared to be pale and chronically, but not acutely, ill. Blood pressure was 110/70 mm. Hg, and heart sounds were normal. The abdomen was scaphoid, and there was a healed left subcostal incision. The liver was palpable 2 fingerbreadths below the costal margin but was not tender. There was no bruit audible in the abdomen on auscultation. Rectal examination was negative.

Laboratory studies revealed hemoglobin 8.2 gm. per 100 cc., red blood cell count 3,380,000 per cubic millimeter, leucocytes 5,450 per cubic millimeter, segmented cells 23%, lymphocytes 71%, monocytes 2%, esinophiles 2%, and basophiles 2%, with a few atypical lymphocytes. Urinalysis revealed no abnormal findings. Blood chemistry determinations revealed total serum protein 7.1 gm., albumin 4.3 gm., globulin 2.8 gm., and blood urea nitrogen 12 mg., per 100 cc., and thrombin time 90%. Sulfobromophthalein tests demonstrated 8% retention of dye in 30 minutes. The Paul-Bunnell test was positive in a dilution of 1 : 14.

Roentgenologic examination of the barium-filled esophagus demonstrated extensive, large varices extending from the midportion of the esophagus to the diaphragm (Fig. 5). The chest was otherwise negative.

An electrocardiogram showed an occasional premature auricular beat and low T-waves suggestive of impaired myocardial function.

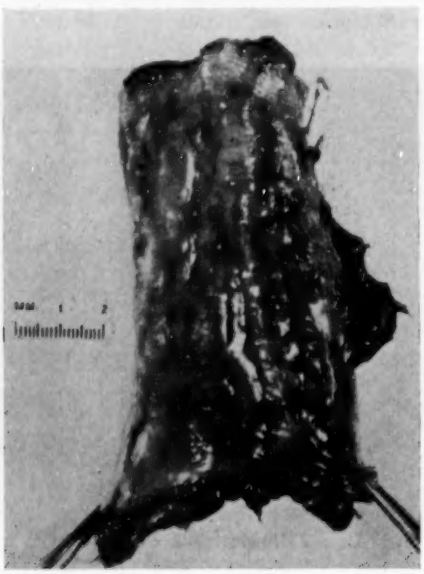

Fig. 6.—Resected specimen in Case 2 showing prominent dilated veins in submucosa of the esophagus.

Several blood transfusions were given in preparation for operation and on March 3 the hemoglobin was 12.3 gm. per 100 cc. and red blood cell count 4,500,000 per cubic millimeter, and her general condition appeared much improved.

Operation was performed on March 10, under endotracheal ether anesthesia. Laparotomy was done through the previous left subcostal incision. Numerous adhesions and dilated veins were encountered in the peritoneal cavity, particularly in the left upper quadrant. The liver was grossly normal in appearance, and a biopsy specimen was obtained. The proximal two-thirds of the stomach was mobilized in the usual manner, and a pyloromyotomy was performed. An anterior thoracotomy incision was made through the fourth intercostal space, and the lung was retracted forward. There were numerous large varicosities, measuring 1 to 2 cm. in diameter, located around the lower esophagus. These were divided and ligated, and the esophagus was mobilized from its bed in the mediastinum. The azygos vein was divided, and after the esophagus was removed an esophagogastric anastomosis was performed in the superior mediastinum. Operation lasted 3 hours 50 minutes and was associated with considerable blood loss, requiring 2,000 cc. of blood by transfusion.

The postoperative course was febrile during the first few weeks after operation. The cause of the fever was not clear, and blood cultures were repeatedly negative. Fortunately, on the 19th postoperative day, the fever spontaneously disappeared, and she improved steadily thereafter. On April 4, 25 days after operation, she was discharged from the hospital.

Pathologic Report.—The specimen of the esophagus was 14 cm. long, and there were prominent dilated veins on the glistening mucosal surface (Fig. 6). Liver biopsy revealed normal architecture of the lobules with definite chronic inflammatory reaction, with scattered polymorphonuclear leucocytes, plasma cells, and an occasional lymphocyte deep in the parenchyma. The histologic findings in the liver biopsy were compatible with mild chronic hepatitis.

At follow-up examination on Oct. 13, 1953, she had experienced no further hematemesis and was feeling much improved (Fig. 7). She complained of abdominal pain following meals and an occasional regurgitation of bile. She had gained 6 lb. (2.7 kg.) since operation. Roentgenograms of the barium-filled esophagus revealed a well-functioning esophagogastrostomy and no evidence of esophageal varices proximal to the anastomosis (Fig. 8).

Fig. 7.—Photograph of patient in Case 2 made seven months after operation showing healed laparotomy and thoracotomy wounds and good state of nutrition. Laparotomy in this patient was performed through the left subcostal incision previously used for splenectomy.

Case 3.—B. B., a 31-year-old white married woman, was admitted to the Methodist Hospital on July 20, 1953, with a history of repeated hematemesis since the age of 8 years. A diagnosis of Banti's disease was made and a splenectomy was performed when she was 9 years old. She had no bleeding for the next four years, but since then she had continued to have almost yearly episodes of gastrointestinal hemorrhage. For the past 18 months the bleeding had been severer and more frequent. One very severe hemorrhage occurred during pregnancy, three months prior to admission, when a Caesarean section was done. Six weeks prior to admission she had another severe attack of hematemesis, requiring 3,500 cc. of blood by transfusion. During her life she had received innumerable blood transfusions, and she had multiple hospital admissions.

Physical examination revealed a well-developed but ill-appearing woman, in no discomfort. Blood pressure was 100/60 mm. Hg. There were no heart murmurs. The abdomen was scaphoid, and there was a left subcostal incision with a moderate-sized incisional hernia. There was a well-healed lower midline scar. The liver was not palpable. No bruits were audible over the abdomen. Rectal examination was negative.

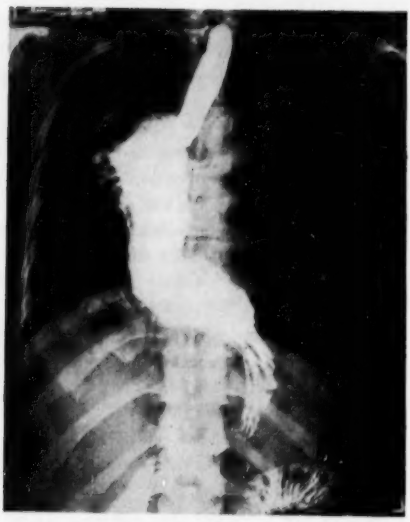

Fig. 8.—Roentgenogram following ingestion of barium in Case 2, showing well-functioning esophagogastrostomy and absence of esophageal varices seven months after operation.

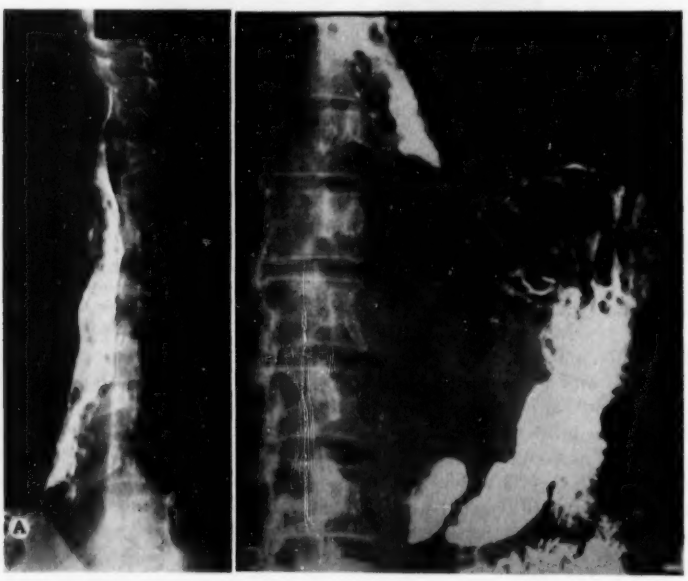

Fig. 9.—Roentgenograms following ingestion of barium in Case 3 demonstrating the presence of varices in the esophagus (*A*) and probably in the cardia of the stomach (*B*).

Laboratory studies revealed hemoglobin 12.2 gm. per 100 cc., red blood cell count 4,300,000 per cubic millimeter, white blood cell count 5,500 per cubic millimeter, segmented cells 40%, lymphocytes 45%, monocytes 5%, and platelets 328,000 per cubic millimeter. Serologic test for syphilis was negative. Urinalysis was normal. Blood chemistry showed serum bilirubin 0.2 mg., total serum protein 7.2 gm., albumin 3 gm., and globulin 4.2 gm., per 100 cc.; thymol turbidity 4 units; cephalin flocculation +1 in 24 hours; alkaline phosphatase 5.6 Bodansky units; prothrombin activity 100% of normal. Sulfobromophthalein test revealed no retention of dye in 30 minutes.

Roentgenographic examination of the esophagus revealed extensive esophageal varices with involvement from the level of the arch of the aorta to the cardia and possible extension into the stomach (Fig. 9). The chest roentgenogram was normal.

Fig. 10.—Photograph of the resected specimen of esophagus in Case 3 showing dilated veins in submucosa.

Operation was performed on July 24 under endotracheal ether anesthesia. Laparotomy was performed first through the previous subcostal incision. Extensive peritoneal adhesions were encountered which were extremely vascular, and they made dissection difficult. The liver was grossly normal. The stomach was mobilized in the usual fashion and pyloromyotomy was done. An anterior thoracotomy incision was made and the lung was retracted forward. In the lower esophagus numerous distended varices were demonstrated, some of which were 1 to 2 cm. in diameter and extended from the level of the azygos vein to the diaphragm. These vessels were divided and ligated, and the esophagus was mobilized from the cardia to a level about 3 to 4 cm. above the azygos vein, and this segment of esophagus was resected. Esophagogastric anastomosis was done in the superior mediastinum, preserving the azygos vein. Closure of the laparotomy incisions involved a rather difficult repair of the abdominal incisional hernia. Operation lasted 5 hours 40 minutes, and during this time 4,500 cc. of transfused whole blood was given.

Postoperative course was relatively smooth, and she was discharged from the hospital on Aug. 4, 11 days after operation.

Pathologic Report.—The specimen of esophagus was 15 cm. long in the fixed state. The mucosa was glistening and rugated, and there were dilated vascular channels visible below the mucosa (Fig. 10).

At follow-up examination several months later, the patient showed steady improvement. She had had no recurrence of bleeding. In a recent communication, Nov. 27, 1953, she stated that she experienced almost no pain after meals, had had no regurgitation of gastric or intestinal juices, and had continued to gain in strength and well-being.

COMMENT

Although it was recognized that the patient in Case 1 was acutely and desperately ill, and therefore an extremely poor surgical risk, operation was finally advised because control of hemorrhage seemed to be imperative. In spite of ample use of vitamin K and other efforts to bolster liver function, there was a pronounced bleeding tendency during and after operation, which was probably a manifestation of hepatic failure. This is further evidenced by the occurrence of hepatic coma as the primary cause of death and is confirmed by the autopsy and histologic studies of the liver, showing extensive necrosis and little normal liver tissue.

Results of Subtotal Esophagectomy in Bleeding Esophageal Varices

Case	Age, Yr.	Sex	Duration of Symptoms (Hematemesis)	Hepato-megaly	Spleno-megaly	Hepatic Impairment	Operation	Results	Final Diagnosis
1 R. P.	11	F	14 mo.	.....	++	Severe	3/2/53 Splenectomy; subtotal esophagectomy	Died 3/22/53 Progressive hepatic failure and coma	Posthepatic cirrhosis and portal hypertension (congestive splenomegaly)
2 E. L.	35	F	3 yr. (Splenectomy, March, 1952)	+ (Mild)	....	None	3/10/53 Subtotal esophagectomy	Improved; no subsequent hematemesis and doing well 9 mo. after operation	Banti's syndrome (mild chronic hepatitis)
3 B. B.	31	F	23 yr. (Splenectomy, 1931)	.....	....	None	7/24/53 Subtotal esophagectomy; repair incisional hernia	Improved; no subsequent hematemesis and doing well 5 mo. after operation	Banti's syndrome

It is probably significant that in both the other patients liver function was relatively normal (Table). This experience, although limited, would suggest that this procedure of subtotal esophagectomy may be applicable primarily to patients with bleeding esophageal varices having relatively little impairment of liver function and that it may be contraindicated in patients with moderate to severe liver disease.

It is recognized that this experience is too small and the follow-up period too short to provide adequate evaluation of the procedure. We are inclined to believe, however, on the basis of the early gratifying results in these few patients and for the reasons indicated above, that it offers a more effective approach to the practical problem of control of hemorrhage, particularly in patients with extrahepatic portal obstruction.

SUMMARY

The control of hemorrhage in esophageal varices remains a serious problem, for which various methods of therapy have been proposed. None of these has provided uniformly satisfactory results, and for this reason another method is proposed, consisting of extensive subtotal esophagectomy, and may offer a more effective approach to the problem.

The rationale of this procedure lies primarily in the more complete extirpation of the main source of hemorrhage.

For a number of reasons the region of the esophagus between the diaphragm and the azygos-vena cava junction may be regarded as the critical zone for esophagogastrostomy in the presence of portal hypertension. Accordingly, it is recommended that the anastomosis after esophagectomy be placed above this zone.

Experience with three cases of bleeding esophageal varices treated in this manner suggests that the procedure is applicable primarily to patients with bleeding esophageal varices having relatively little impairment of hepatic function.

NOTE.—Since this presentation was made, the patients in Cases 2 and 3 have been seen in follow-up examination on May 20, 1954. Both are doing well, have gained weight, and have experienced no further bleeding.

DISCUSSION

DR. JACOB K. BERMAN, Indianapolis: I must confess that when Dr. Cooley asked me to discuss this paper it was my reaction that Drs. Cooley and DeBakey were employing drastic procedures. However, radical measures are often necessary to control a fatal disease, and if this operation will stop the recurrence of exsanguinating hemorrhage it should be used.

Dr. Tuttle and Dr. Cooley have stated that subtotal esophagectomy may be useful in extrahepatic rather than intrahepatic venous obstruction. I certainly agree that the operation would not be indicated in advanced portal cirrhosis, because the causative mechanism is an obstruction in the hepatic venous outflow. Removal of the esophagus would not stop the formation of varices in other portions of the gastrointestinal tract.

The cause of esophageal varices and the cause of bleeding are not definitely known, and, as Dr. Cooley indicated, perhaps the erosive factor is very important. Indirect and direct operations have not yielded good results thus far.

The veins of the thorax and abdomen do not contain valves except for the azygos and testicular. Moreover, the valves in the azygos system are imperfect. Perhaps remedial measures might be directed toward the improvement or creation of valves in the azygos system. Rarely the vena cava is occluded by fibrosis or compressed by a tumor or cyst. Relief of the obstruction may stop the esophageal bleeding.

If bleeding is due to erosions in the esophagus, then a modest esophagectomy will do no more good than partial gastrectomy in hemorrhagic gastritis. It requires practically a total gastrectomy to stop the hemorrhage, and the same may be true in the esophagus.

I shall await with great interest a follow-up report on this very interesting innovation.

DR. DENTON A. COOLEY, Houston, Texas: I tried to emphasize the significance of impairment in hepatic function in selection of patients for this operative procedure. This procedure is fundamentally an attempt to control bleeding from the esophagus and probably does not influence portal tension at all.

In the manuscript we referred to the possible use of temporary phrenic paralysis to relieve acute bleeding in the patient with advanced cirrhosis. The rationale of such a procedure is entirely speculative at this time.

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RESULTS OF SURGICAL TREATMENT OF CARCINOMA OF THE ESOPHAGUS AND GASTRIC CARDIA

Follow-Up Study

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TWENTY years have elapsed since Ohsawa [1] (cited by Bird [2]) first successfully resected the esophagus for carcinoma and reestablished gastrointestinal continuity, a procedure introduced into this country by Adams and Phemister [3] in 1938. Limited at first to resection of carcinoma of the gastric cardia and to lesions of the lower esophagus, the range of operability was markedly extended in 1944 by Garlock,[4] who suggested transplantation of the esophagus above the arch of the aorta and the establishment of an anterior anastomosis between the stomach and the esophagus. As would be expected, the main surgical interest during these years was focused upon problems of operative technique. Due chiefly to the extensive experiences of Garlock,[5] Sweet,[6] Strieder,[7] Payne and Clagett,[8] and others, certain technical details have become established and the operative hazards decisively lowered, the net result being an increase in the resectability rate accompanied by a decrease in the mortality rate. Accomplishments thus far would seem to indicate that a patient could be offered a resection of his tumor with a reasonable degree of safety. Similarly, in carcinoma of the cervical esophagus, the early work of Wookey [9] and Watson and Pool [10] has been applied and extended by others.[11] Grimes and Stephens [12] have reported 17 such cases with operation in which 12 patients were alive for periods varying from 1 to 36 months after surgery.

Recently, however, the center of interest has changed, and more attention is being directed to the results obtained from such operative procedures. Some, like Ravitch, Bahnson, and Johns,[13] are profoundly disappointed in the results; others, such as Wangensteen * and Gibbon, Allbritten and Templeton [15] are still hopeful.

In our own section of the country, Jarvis [16] recently reported the results of a survey of the experience in the city of Seattle. Since 1946 there had been 30 patients operated upon with carcinoma of the esophagus. No single patient survived beyond a two and one-half year period. Such a pessimistic report prompted a review of our own cases, the results of which are reported below.

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Read at the Sixty-First Annual Meeting of the Western Surgical Association, Chicago, Dec. 5, 1953.

* Wangensteen, in discussion on Pool.[14]

CLINICAL MATERIAL

The series of patients available for study is composed of 54 patients with carcinoma of the esophagus or gastric cardia, treated at the University of Oregon Medical School, at the Veterans Hospital, and in private practice. In 28 patients

TABLE 1.—*Summary of Data (Total Cases, Fifty-Four)*

Carcinoma of Esophagus		26
Carcinoma of Cardia		28
Not Operated	Exploration Only	Resection and Anastomosis
9	10	35

TABLE 2.—*Site of Lesions and Effect upon Resectability and Operation Mortality Rates*

	NOT OPERATED	EXPLORATION NOT RESECTED	RESECTED	DEATHS	MORTALITY RATE
Ca Esophagus	5	6	7	2	28.6%
	–	3	5	1	20%
	5	9	12	3	25%
Ca Cardia	2	3	23	5	21%
TOTAL	7	12	35	8	22.8%

TABLE 3.—*Age Incidence*

AGE	CARCINOMA OF ESOPHAGUS	CARCINOMA OF CARDIA	TOTAL
30-39	–	1	1
40-49	1	–	1
50-59	6	5	11
60-69	10	9	19
70-79	7	11	18
80-89	2	2	4

the carcinoma was primarily gastric, an adenocarcinoma secondarily invading the esophagus. In 26 patients the primary site was the esophagus; all were epidermoid carcinoma. Of the 54 patients, 7 were not operated upon; 12 underwent exploration, not resection, and in 35 the growth was resected and gastrointestinal continuity reestablished, with a resectability rate of 65% (Table 1). The mortality rate is indicated in Table 2.

The ages of the patients are indicated in Table 3. The youngest patient was 37; four patients were more than 80. Only 13 patients were under 60 years of age, 40 being 60 or more. Successful resections were carried out in 8 patients who were 70 years or more, 6 being more than 75. In the group of patients in whom resections were not carried out, the ages varied from 60 to 88 years, with an average of 74 years.

The presenting symptoms were the ones usually recorded; dysphagia, substernal or epigastric distress, and weight loss, 10 to 40 lb. (4.5 to 18 kg.) being the usual amount. In two instances the occurrence of mild upper gastrointestinal hemorrhage was the first indication. So impressed have we been with the importance of the onset of dysphagia as a definite entity that we have been willing to subject to surgical exploration any patient presenting that symptom, in spite of the fact that barium studies may be negative and repeated endoscopic examination may not be revealing. In one such instance the dividend of following such a policy was the discovery, not of a carcinoma of the cardia as had been suspected, but of an early resectable carcinoma of the tail of the pancreas producing dysphagia by direct pressure upon the cardia.

DIAGNOSIS

A serious attempt has been made to establish early diagnosis, but, unfortunately, a review of the cases indicates the same difficulties existed that are encountered

TABLE 4.—*Diagnosis in Group with Resection*

Roentgen Ray		Endoscopic			Biopsy		
		Not done	11		Not done	17	
		+	−		+	−	
34	1	18	6		14	4	

elsewhere. The duration of symptoms varied from three weeks to three years, the average being five and three-tenths months. The average duration of symptoms in the group without resection, those in whom extensive carcinoma was present, was five and eight-tenths months, or essentially that found in the group with resection.

Earlier it was considered mandatory that endoscopic examination be carried out. For a number of reasons this attitude is no longer entertained. The diagnosis is usually apparent in the initial roentgen examination, a fact mentioned by Gibbon, Allbritten, and Templeton.[15] Also, as reported in his series, the diagnosis was overlooked by the roentgenologist in only one instance in this series (Table 4). On the other hand, four patients, when first seen, had had esophageal dilatations carried out for periods of seven to nine months because repeated endoscopic examinations had not supported the diagnoses which were actually inherent in each instance in the roentgenograms of the initial barium studies. In addition, perforations by the esophagoscope occurred in two patients with carcinoma of the cardia.

We are beginning to believe that while esophagoscopy is of great aid in doubtful cases, it is of questionable value in patients with typical findings and may even be dangerous. Negative biopsies should not contraindicate, nor should they delay, exploration. By the same token, a sense of resistance encountered at the cardia as the gastroscope is being passed, in the hands of a skilled examiner, should be

regarded as indication for exploration. Further, one should comment that in lesions of the mid or upper esophagus the importance of bronchoscopy could scarcely be overestimated.

OPERATIVE DETAILS

All of the operative procedures were carried out through a left thoracic approach; in carcinoma of the cardia a transverse abdominal extension has occasionally been subsequently added in order to facilitate nodal dissection in the region of the left gastric artery. The technique of anastomosis is essentially that described by Kirklin and Clagett,[17] the lesser curvature portion of the severed end of the stomach being closed and the esophagus anastomosed to the remaining section. In the seven patients with carcinoma of the midthoracic region, the anastomosis was carried out anterior to the arch of the aorta. In this group there were two operative deaths, each due to congestive atelectasis. Of the 23 patients with resections for carcinoma of the cardia, total gastrectomy was performed in 6, with reestablishment of gastrointestinal continuity by means of the Roux-Y type of esophagojejunostomy. On occasion, other organs have been included in the resection—the spleen in nine instances, the pancreas in four, left lobe of the liver once, and on two occasions the left adrenal was included in the excised specimen. In spite of the advanced age of the majority of the patients and the magnitude of the procedure, the average patient has withstood the operation well.

Subsequent additional operative procedures became necessary in three patients. A pyloroplasty of the Heineke-Mikulicz type was carried out twice, once three months following resection of a lower esophageal growth and once following resection of carcinoma of the cardia. A third operation was an ill-advised attempt to drain a sizeable gastric remnant by means of a gastroenterostomy. This was finally taken down and the gastric remnant resected.

In preoperative preparation greatest emphasis has been placed upon multiple blood transfusions. The parenteral administration of vitamin supplements and the preoperative use of antibiotics are routinely necessary. Preoperative jejunostomy has been carried out on four occasions, but in each instance the result has been disappointing, and this has almost been abandoned. Because of the frequency with which cardiac irregularities have occurred either during surgery or in the early postoperative period, all patients are now either digitalized or given quinidine preoperatively. Digitalization does not need to be carried to excess, as rapid digitalization may be quickly effected postoperatively by intravenous means.

OPERATIVE MORTALITY

In the series of 35 operations there were 8 operative mortalities; the cause of death is shown in Table 5. Five fatalities followed resection of the cardia: One occurred after resection of the lower esophagus, and two occurred in lesions at or above the arch of the aorta (Table 2). One of the two patients who died of massive pulmonary embolism had been operated upon 36 hours following posterior perforation, just proximal to a carcinoma of the cardia during esophagoscopy. The second followed resection of a lower esophageal lesion. In each, the source was an extensive phlebothrombosis of the calf veins.

Two patients died of a leak in the anastomosis—these we believe due to technical errors—both occurred in the early years. In one, no residual carcinoma was found

at autopsy. The fifth patient died of massive mediastinal and pleural infection, no leak of the anastomosis being demonstrated at post mortem. Prolonged and difficult operations were carried out in two patients in whom the lesions lay behind and above the arch of the aorta. In each instance the lungs became cherry red in appearance and quite firm. Progressive cyanosis ensued, and the patients died, with autopsy findings of congestive atelectasis.[18] The last death occurred in a patient 73 years of age who had survived two previous episodes of coronary thrombosis. He died of myocardial infarction on the third postoperative day.

TABLE 5.—*Hospital Deaths*

CAUSE OF DEATH	NO CASES
Leak of Anastomosis Mediastinitis Empyema	2
Pulmonary Embolism	2
Pulmonary Edema Congestive Atelectasis	2
Myocardial Infarction	1
Mediastinitis, Atelectasis Bilateral Pleural Effusion	1

TABLE 6.—*Survival Time After Operation, in Months*

1947	7	8	20			
1948	4	9	16	(53)	(56)	
1949	8	10	11	11	(41)	
1950	4	4	5	10	17	(33)
1951	4	8	11	14	(19)	(15)
1952		(5)	(12)			

NOT OPERATED	½	¾	1	2	2	3				
EXPLORATION ± JEJUNOSTOMY	¼	½	1	1	1	1	1	2	2	2	2 2

O-indicates still living
— = Xray therapy

RESULTS

In the entire group of 56 patients, 7 were not operated upon, 12 underwent exploration but not resection, and 35 had resection and the anastomosis completed—a resectability rate of 65%. In the group of 35 patients operated on, there were 8 hospital deaths, leaving 27 patients to be followed.

This represents exactly half of the group who originally presented themselves for treatment. Of these 27 patients who successfully survived the operative procedure, 8 are still alive (Table 6); 4 are long-term survivors; 1 patient is living and well 56 months following resection of a carcinoma of the midthoracic esophagus, and 3 are living, 53, 41, and 33 months, respectively, following resection of car-

cinoma of the cardia.† Since this series began in 1947, the time elapsed is too short to record five-year results, but of the group operated upon before 1950, there are three patients, or 23%, who have survived the three-year period. This represents, however, only 13% of the total number of patients seen during those years.

In terms of palliation, the over-all mean palliation achieved has been 15.7 months. This includes all patients who survived their resections. The number of months that each patient survived is shown in Table 6. The figures that are circled indicate the number of months that patients still living have so far survived. If one excludes the long-term survivors, the mean palliation achieved in the group who have already died is only 10 months. In the group of patients operated upon before 1950, the general over-all palliation was 19.6 months.

CARCINOMA OF THE ESOPHAGUS

In this small series of patients, we have found, as have others, that our greatest disappointments have been encountered in that group of patients in whom the lesions lay at or above the arch of the aorta. (No patients with carcinoma of the cervical esophagus are included, as our experience is limited to four.) Here, the greatest number of patients were encountered whose disease had progressed too far to warrant exploration. There were five such patients. The contraindications to exploration were tracheoesophageal fistula in two patients, distant metastases in one; one patient died of massive gastrointestinal hemorrhage on the 12th hospital day, and the remaining patient, with an extensive lesion, was treated by roentgen therapy but received only 2,400 r, pursuing a steady downhill course. All patients in this group died within the three-month period.

In the group with exploration (13), resection was completed in only 7, the contraindications to resectability being direct invasion of adjacent structures—left lung, trachea, left main-stem bronchus, or to massive nodal involvement. Jejunostomy or gastrostomy was performed in five of the seven instances, but the periods of survival were very brief. Three patients died within the month, the longest survivor lived for three months.

Thus, in this segment of the esophagus, we completed resection and anastomosis in only 7 of 18 patients, a resectability rate of 46%.

In the group with resection, five patients survived their operations, and their fate is as follows: Three patients have survived for periods of 5, 19, and 56 months, respectively, and two have died, having lived 4 and 14 months after surgery.

With carcinoma of the lower esophageal segment, eight patients were seen. Exploration was done in all cases, and five patients underwent resection. Four survived their operations. They have since died, having lived periods of 10, 10, 16, and 17 months, respectively.

Viewed as a group of patients operated upon for carcinoma of the esophagus, irrespective of site, the average short-term palliation achieved was 13.4 months. Only three patients are still living, and in each the disease lay in the middle third. The following case is our only long-term survivor.

CASE 1 (M. N. 60887).—Survival period 56 months.‡ Carcinoma of midthoracic esophagus. Partial esophagectomy; anterior (aorta) esophagogastrostomy (Fig. 1).

† See Addendum.

‡ See Addendum (patient has now been alive and well five and one-half years).

Patient aged 58 years. Had dysphagia three months. Weight loss 38 lb. (17 kg.). Roentgen ray examination: carcinoma involving the esophagus from the level of the arch of the aorta to 2 in. (5 cm.) proximal to the ampulla. Esophagoscopy: nodular, sloughing mass in midportion of the esophagus. Biopsy: squamous-cell carcinoma.

Operation July 27, 1948: left thoracic approach. Tumor involving esophagus for approximately 9 cm. extending from beneath the arch of aorta distally. No obvious metastases. Resection of the esophagus with esophagogastrostomy carried out anterior to the arch of the aorta. Accidental tear of right mediastinal pleura.

Pathology: epidermoid carcinoma completely involving the esophagus for a distance of 8.5 cm. Moderate differentiation. Proximal free margin measured 2.5 cm.

Fig. 1 (Case 1).—Esophogram indicating location and extent (8.5 cm.) of carcinoma of the esophagus.

Postoperative course: normal until 30th postoperative day, when a gastropleural fistula developed at upper angle of thoracic wound. Roentgenogram of chest revealed no empyema or fluid in the left chest. Spontaneous healing two months later.

Subsequent course: Patient was seen at frequent intervals at Tumor Clinic. On Sept. 21, 1951, four years later, he was within 5 lb. (2.3 kg.) of preoperative weight. In October, 1952, he was admitted to hospital for shortness of breath and signs of myocardial failure, responding to digitalis. X-ray examination and esophagoscopy revealed no recurrence. Patient again discharged and has been well since.

CARCINOMA OF THE CARDIA

Twenty-eight patients with carcinoma of the cardia were seen. In two with advanced disease, exploration was not done; one lived three weeks and the other one month. Exploration was done in three patients, but because of extensive dis-

ease, resection was not done. All died within a two-month period. Thus, of 28 patients, resection and anastomosis were completed in 23, a resectability rate of 82%. There were five hospital deaths, a mortality rate of 21%.

Mean palliation achieved in the 18 surviving patients was 14.6 months. Three patients might be designated as long-term survivors. They are living at periods of 53, 41, 33 months, respectively. The histories of these three patients are briefly abstracted below. Exclusive of these three patients, the remaining group, all of whom have since died, reached a short-term survival rate of just under 9 months.

REPORT OF CASES

CASE 2 (B. L. B. 120999).—Survival period 53 months.§ Carcinoma of the cardia. Partial gastrectomy and esophagectomy; esophagogastrostomy; splenectomy.

Man, aged 75. Anorexia one month. Proved coronary thrombosis 10 years previously, fairly well compensated. Roentgen examination: carcinoma of the cardia involving lesser curvature. Gastroscopy and esophagoscopy: tumor not visualized.

Operation, Oct. 28, 1948: abdominothoracic approach. Adenocarcinoma of cardia 4 by 5 cm. Carcinoma found in only one of the left gastric group, and one node of gastrocolic omentum was replaced with carcinoma.

Postoperative course: Patient tolerated operative procedure well and by the eighth day was eating a soft diet. Dismissed on 15th day.

Subsequent course: Two months later patient weighed 135 lb. (61 kg.) but was eating only with difficulty. One year following this, he maintained his weight and was eating regularly. On July 16, 1950, he fell out of cherry tree while gardening and was admitted to hospital with symptoms suspicious of subdural hematoma. Now, at 80 years of age, still does odd gardening jobs. His weight is 129 lb. (58.5 kg.) and he eats well.

CASE 3 (C. H. 88639).—Survival period 49 months. Carcinoma of cardia. Partial gastrectomy and esophagectomy; esophagogastrostomy, and (later) lower left lobectomy; excision of stenotic stoma and reanastomosis.

Man, aged 54. Dysphagia five months. Occasionally, black tarry stools. Roentgen examination: large filling defect at cardioesophageal junction. Absent free hydrochloric acid. Esophagoscopy and biopsy revealed adenocarcinoma. Weight, 155 lb. (70.3 kg.).

Operation, July 12, 1949: left thoracic approach. Growth was found to involve distal 2 in. of the esophagus and proximal ½ in. (1.3 cm.) of the cardia. No enlarged mediastinal glands found, and the pathological examination of the resected stomach and esophagus revealed no involved nodes. The right pleura was opened in the dissection. In the resected specimen the tumor measured 6.6 by 4.8 cm., an adenocarcinoma involving the esophagus.

Postoperative course: uneventful.

Subsequent course: Readmitted to hospital on Aug. 26, 1949, for open drainage of left empyema cavity containing 90 cc. of fluid. Approximately two years later weight was 130 lb. (59 kg.). Because of mild dysphagia, a biopsy of the anastomotic area was obtained—no carcinoma found. Three years later a stenosis had developed at the site of the anastomosis. Biopsies again were negative; consequently, regular dilatations were carried out up to 45 F. Thirty-seven months postoperatively a shadow appeared in the lower lobe of the left lung. Six months later, shadow measured 4 by 5 cm.; no other shadows were visible. Left lower lobectomy was carried out on April 9, 1953 by Dr. John Higginson. Mass measured 4 by 2 by 2 cm., a metastatic adenocarcinoma in the basilar portion of the left lower lobe. No enlarged nodes were found at the hilum. The stenotic stoma of the previously carried out anastomosis was excised and stomach and esophagus reanastomosed. Three months later the patient had gained 35 lb. (16 kg.).

Comment: Patient is alive and well eight months later.

CASE 4 (O. K. 87183).—Survival period 36 months. Carcinoma of the cardia. Total gastrectomy; partial esophagectomy; partial pancreatectomy; splenectomy, and Roux-Y anastomosis.

§See Addendum. Alive and well 10 months later, this patient has survived the five-year period.

Patient aged 74. Epigastric distress and vague pain of three weeks' duration. No dysphagia, nausea, or vomiting. Weight loss 20 lb. (9 kg.). Roentgen ray examination: partially constricting lesion of lower esophagus with filling defects in the cardia. Also calcified densities in the gall-bladder area. Esophagoscopy revealed carcinoma, and biopsy, adenocarcinoma.

Operation, June 7, 1950 (Dr. Clare Peterson): Lesion of the cardia 4 cm. in diameter was found to involve regional nodes about the left gastric artery. One nodule in the tail of the pancreas and suspected nodes along the splenic artery. No metastases demonstrated in the liver. No free peritoneal fluid. Total gastrectomy with resection of the lateral third of body and tail of pancreas, the spleen, and the gastrocolic and the gastrohepatic omentum. Esophagus resected 4 in. (10 cm.) above the diaphragm. Gastrointestinal continuity reestablished by Roux-Y type of anastomosis.

Pathology: adenocarcinoma of cardia involving esophagus. Of 50 nodes examined in the area of the celiac axis and left gastric artery, 10 were replaced with carcinoma. Nodes of the gastrosplenic ligament and splenic region were not involved. The mass was adherent to but had not invaded the pancreas.

Subsequent course: Postoperatively patient continued to lose weight for three months. He then began to gain weight slowly. Thirty-three months later he was doing odd gardening jobs and eating well.‖

EFFECT OF METASTASES

As judged by the surgical findings at the time of resection, 23 of 35 patients demonstrated lymph node involvement, an incidence of 65%. In carcinoma of the cardia there were only six patients in whom metastases were not demonstrated. The fate of these patients is of some interest. Two are still living and apparently well, one at 41 months and one at 14; four have died at periods of 8, 11, 11, and 20 months; two patients died of massive liver involvement; in a third, although no autopsy findings are available, carcinoma had been demonstrated in the gastric remnant by roentgen examination, and the fourth patient died with disease limited to gastric remnant. One may wonder if the surgeon had been more aggressive in these last two patients, carrying out total gastrectomy instead of subtotal, would the outcome have been different?

Of 12 patients who did have demonstrable metastases and who survived their operation, 3 are living and well at periods of 53, 33, and 12 months. Of the remaining nine, all are dead. One patient, a man of 75 years with known heart disease, died five months after surgery under circumstances typical of myocardial infarction. No autopsy was performed, and it is therefore possible that he did not have carcinoma, as he had been well; but, if so, this is the only patient in this group. The other eight are known to have died of widespread carcinoma. The average survival time was six and six-tenths months.

Somewhat similar findings were encountered in carcinoma of the esophagus. In six patients, glandular involvement was demonstrated; in six it was not. It was interesting to note that the glands most commonly found involved in carcinoma of the upper thoracic esophagus were those of the celiac group.

In the group with glandular involvement 5 of 6 patients survived the operative period; all have since died of extensive carcinoma at periods of time of 17, 16, 14, 10, and 4 months postoperatively.

‖ Subsequent survey carried out after preparation of paper—patient had developed dysphagia, and, although he had survived the three-year period, the presumptive diagnosis was persistent carcinoma.

By contrast, in the group in whom nodal involvement was not demonstrated, three of four patients who survived the operation are still alive and well at periods of 56, 19, and 5 months. The remaining patient died at 10 months, of hemorrhage following perforation of carcinoma of the gastric remnant into the aorta.

COMMENT

Current medical reports indicate a certain pessimistic attitude in regard to the effectiveness of surgical therapy in treatment of this form of carcinoma. There is no doubt as to the justification of such an attitude in regard to long-term survivals. Very few five-year arrests of carcinoma of the cardia have been reported. Gibbon and his associates [15] in an excellent report did not mention any such survivals. Humphreys and Moore [19] reported on one patient living and well seven years after resection of adenocarcinoma of the cardia. Sweet,[20] with his most extensive experi-

TABLE 7.—*Survival of Patients Treated by Resection and Anastomosis (Thirty-Five Cases)*

	TOTAL	CARCINOMA OF CARDIA	CARCINOMA OF ESOPHAGUS	
			MIDDLE THIRD	LOWER THIRD
Number of operations	35	23	7	5
Operative deaths	8	5	2	1
Recovered from operation	27	18	5	4
Survived 6 months	21	14	3	4
Survived 1 year	11	6	3	2
Survived 2 years	4	3	1	0
Survived 3 years	3*	2*	1	0
Survived 4 years	2†	1†	1†	0

* Ten months later - has survived 4 yrs.
† Ten months later - has survived 5 yrs.

ence, has reported on 11 patients out of 147 who survived five years or more. To this group we may now add one.

Five-year survivals of carcinoma of the esophagus are even more rare. In the three reports quoted above there is only 1 such patient, reported on by Sweet, representing the total salvage of 107 patients operated upon. To this group we may now add one more, the details of which have been quoted.

However dismal the long-term results may be (Table 7), the degree of palliation actually achieved is very satisfactory. Though his period of life may be short, the patient is able to eat, swallow, and live comfortably. On the average, the postoperative weight levels have been maintained, but ordinarily the original weight is not regained. Of equal importance is the fact that the onset of recurrent dysphagia, indicating the presence of persistent carcinoma is usually very close to the terminal event, the final period of illness being very short.

In estimating the effectiveness of this type of therapy, consideration should be given to other types of therapy currently available. Gastrostomy ¶ alone has been

¶ References 13 and 21.

almost universally unsatisfactory. In the group of patients under consideration, gastrostomy or jejunostomy was carried out five times, as previously mentioned, with little attending benefit.

Other types of palliation may be offered, such as excision of the growth and restoration of gastrointestinal continuity by means of plastic tubing (Berman [22]) or by by-passing the obstructed segment by use of a long jejunal loop placed either subcutaneously (Ravitch and his associates [13]) or brought up through the anterior mediastinum (Robertson and Sargeant [23]). Outside of Robertson's # comments upon fate of eight such patients, follow-up studies are not currently available by which to judge the effectiveness of such therapy.

A third alternate form of palliative therapy is that of roentgen ray treatment. Rather extensive experience has been reported by Scandinavian authors,* a group of some 795 patients having been studied. Long-term survivors are rare—one

Fig. 2.—Esophogram for heart size, in a patient aged 74 who was admitted with moderately severe dyspnea and orthopnea of two weeks' duration. There were no symptoms referable to the growth. The tumor lay just below the arch of the aorta. No fixation to surrounding structures. Postoperative death of congestive failure. Autopsy revealed three peritracheal lymph nodes in the right chest replaced with carcinoma. This indicates the extent to which the disease may progress without producing a single symptom. (Patient of Dr. Carleton Mathewson Jr., of Stanford University; illustration is reproduced by his permission.)

reported by Krebs and his associates [24] and five by Gynning.[27] In almost every series, short-term palliation averaged about eight months. In regard to the effectiveness of the palliation, approximately 50% of the patients evidently were able to eat a normal or only slightly restricted diet, while the remaining 50% were limited to puréed foods or to liquids. Of other reports,† the most enthusiastic in the country is that of Buschke and Cantril.[30] They have recently summarized the results of treatment of 58 patients with carcinoma of the esophagus over a 12-year period. Three are living periods of 12, 10, and 8 years; two others, periods of 2 and 3 years.

Robertson, in discussion on Ravitch, Bahnson, and Johns.[13]

* References 24 to 27.

† References 28 and 29.

A group of eight achieved palliation of an average of 12.7 months. Although no survival periods are mentioned regarding the remaining 45 patients, the long-term results are impressive.

In the hope of attaining better end-results, much stress has been placed on early diagnosis. Brewer ‡ has stressed the intermittency of the early dysphagia and its possible relief by medication. Actually, in this series, our greatest disappointments have been those patients who have had symptoms for only a few weeks with subsequent operative findings of widespread carcinoma, possible examples of the biological predeterminism of the tumor as discussed by MacDonald.[31] It is possible that false hopes may have been built around the thought of early diagnosis. An example of the progress of the disease to actually an incurable state, because of metastases, is shown in Figure 2. This is a reproduction of a roentgenogram published by permission of Dr. Carleton Mathewson, of Stanford University, and depicts the extent to which a carcinoma may grow before any symptoms at all are present.

Of great interest recently are the attempts to extend the scope of resectability by operations through the right chest, as originally proposed by Lewis [32] and MacManus.[33] By such an approach, Mathewson § has reported 100% resectability, tumor being left behind if necessary. This combined with supervoltage roentgen ray therapy of the residual tumor might well be of some benefit. Adams and his associates [35] have mentioned such postoperative roentgen ray therapy, and their results will be of great interest.

SUMMARY

A summary of a small group of 54 patients with carcinoma of the esophagus and the cardia has been undertaken, and the results in terms of months of palliation achieved by operative procedures are submitted. Two cases are reported of patients who are living and well five years after resection of carcinoma, one of the cardia and one of the esophagus.

ADDENDUM

As this survey was initiated 10 months ago, 10 months may be added to the survival periods. The three long-term surviving patients are alive and well. Case 4 died after two months of increasing dysphagia, presumably of persistent carcinoma. He had lived three and one-half years.

DISCUSSION

DR. HOWARD K. GRAY, Rochester, Minn.: I had not planned to discuss this paper, but I am happy to do so. Dr. Chauncey and I had great fun working together some years ago, and I am perfectly delighted to see the interest he has taken in this field.

When I hear someone discuss radical procedures with such unhappy end-results as a whole, I can not help but wonder whether or not we may be overlooking some factors in the handling of patients which may be classified, roughly, under the heading of economic factors. Are we justified in imposing these procedures on patients when we know that the end-result is so unsatisfactory in such a high percentage of cases? Are we justified from the point of view of the expense incurred, the time incurred, the distress that we impose upon them, and the risk? In other words, do we have a right to impose these factors on 99 patients to save 1? I do not know that we have, in many instances, and I think perhaps we should take stock of ourselves a bit when we are considering the radical type of radical operation.

‡ Brewer, in discussion on Gibbon, Allbritten, and Templeton.[15]

§ Reference 34, and Mathewson, in discussion on Gibbon, Allbritten, and Templeton.[15]

The primary lesions in the esophagus were the most unsatisfactory ones. The primary lesions in the cardia of the stomach with secondary invasion of the esophagus proved to be more encouraging, and in these, perhaps, there is greater justification for radical operation. I, personally, have become extremely discouraged, as so many others have, with the problems presented by primary carcinoma of the esophagus, and have limited surgical exploration to a relatively small and carefully selected group of patients.

DR. LESTER R. CHAUNCEY, Portland, Ore.: During the 15 years which have elapsed since Drs. Adams and Phemister (of this city) introduced the operation into this country, there has been a great deal of interest shown in the technical aspects of the operative procedure. To mention one such, for example, the advisability of a right or left thoracic approach has been debated at length. However, relatively little attention seemingly has been paid to the end-results obtained and to such problems as those which Dr. Gray has mentioned. In fact, it was with these questions in mind that the present study was undertaken.

I would certainly agree with Dr. Gray that the danger of producing an economic as well as a gastric cripple is a very real one, and certainly in each individual case one must balance the benefits offered by the roentgenologist against those offered by the surgeon. A report of the latter is likely to have a very sobering effect upon one's enthusiasm. However, at the present time, I know of little else we have to offer, and even today we may offer an occasional patient a relatively long period of palliation.

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LYMPHOSARCOMA OF GASTROINTESTINAL TRACT

Analysis of Five Cases

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URBANA, ILL.

FIVE PROVED cases of lymphosarcoma of the gastrointestinal tract occurring in adult patients were treated at the Carle Hospital Clinic in the five-year period from 1947 to 1953. These cases are reviewed for the purpose of pointing out certain characteristic features of the disease. Although unrecognized findings suggestive of lymphosarcoma were present in some of the cases, in none was the correct diagnosis made before histological studies of the tissues were completed.

The stomach was the site of the tumor in two cases, the appendix and ileocecal region in one, the descending colon in one, and a unique involvement of the entire colon in one. A biopsy for diagnosis was the extent of the surgery in this case. A preoperative diagnosis of carcinoma was made in each of the first four cases.

The reported incidence of lymphosarcoma of the gastrointestinal tract relative to that of carcinoma varies from 1 : 100 to 1 : 50. The significant figures of McSwain and Beal [6] show a ratio of 1 : 51 of gastrointestinal malignant lymphoma to carcinoma in 149,469 admissions to the New York Hospital from 1933 to 1942.

The stomach seems to be the commonest site of occurrence, with the ileocecal area a close second. In 1949, Singleton and Moore found more than 563 cases of gastric lymphosarcoma reported in the literature. The intestinal tract up to the same time was involved in 535 reported cases, as compiled by Charache [2] in 1943 and by Singleton and Moore [7] up to 1949. The colon and rectum are much less frequently involved than the stomach and ileocecal areas. Lymphoid lesions of the large intestine, other than the rectum and anus, are more likely to be malignant than benign.[3]

Males are much more prone to have lymphosarcoma of the gastrointestinal tract than females. In the stomach alone the incidence may be as high as 6 : 1.[5] In adults the average age is somewhat lower than in cases of carcinoma, but in most series the difference is not appreciable.

Lymphosarcomata in the gastrointestinal tract arise from the lymphoid elements of the submucosa and may be primary or a part of a generalized systemic disease. Anderson [1] distinguishes between two major types of malignant lymphomata, which are reported in approximately equal numbers. They are the small and large round-cell lymphosarcoma (malignant lymphocytoma and lymphoblastoma) as one group and the reticulum-cell sarcoma as the other. The latter type arises from the supporting stroma of lymphoid tissue, the reticulum cells. The former, the small and large round-cell lymphosarcoma, appears in the germinal centers of lymph follicles and

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is the immediate descendent of lymphoblasts mothered by specialized reticular cells. Malignant change may occur at any stage of differentiation, with several phases often represented in a single tumor.

A patient who appears to be in good general condition but who has a palpable abdominal mass and symptoms referable to the gastrointestinal tract should arouse one's suspicion of lymphosarcoma. The tumor arising in the submucosal lymphoid structures apparently extends more longitudinally than circumferentially. Thus, there results a bulkier mass which, if it obstructs, usually does so by encroaching upon the lumen without mucosal ulceration.

There is no reliable roentgenographic aid in establishing the diagnosis.[9] However, x-ray evidence of a large lesion in relation to short duration of symptoms which are milder than is compatible with the x-ray and physical findings may suggest the diagnosis of lymphosarcoma. Laboratory tests, including hematological procedures, are noncontributory and commonly are within normal range.

In the treatment of malignant lymphomata of the gastrointestinal tract, surgical excision of the tumor and the involved regional nodes is generally preferable, the more encouraging reports being in the gastric group.* Radical excision of uninvolved lymph nodes well beyond the site of the tumor is usually deemed unnecessary. Although extension of the tumor to the regional nodes does occur, the site or sites of metastatic involvement often defy all concepts of pathologic physiology and anatomical reasoning of tumor spread.

In those cases in which involved nodes must be left behind or there exists a hopelessly nonresectable lesion, radiation therapy is indicated. Biopsy should always be done in cases of extensive malignant change in the abdomen when explored surgically. Occasionally what appears to be a carcinoma grossly may, in fact, be lymphomatous and, therefore, sensitive to irradiation. Somewhat better results have been reported in the small-cell type.† Metastatic lesions are best treated by irradiation as they occur. Recurrences are usually distant and not local. Therefore, prophylactic treatment by x-ray has not proved practical because of the inability to anticipate the sites of metastatic spread.

The following five cases are being reported with only the significant data listed in each case.

REPORT OF CASES

CASE 1.—In a 46-year-old man (Fig. 1), clinical evidence of gastric bleeding indicative of mucosal ulceration did not appear for two years after the onset of symptoms of epigastric distress. There was the roentgenologic finding of marked deformity and narrowing of the distal one-third of the stomach. In spite of such extensive gastric involvement, the patient had lost little weight and his nutrition was good.

A high gastric resection, well above the involved portion of the stomach, was carried out. Many nodes deep in the upper abdomen and about the pancreas and celiac areas were not removed. Therefore, x-ray therapy was given postoperatively. The diagnosis of small-cell lymphosarcoma was somewhat encouraging as to the amount of palliation expected. The patient is alive and well two years after surgery.

CASE 2.—This patient, (Fig. 2), a 51-year-old butcher, came to the Clinic because of crusting of the lower lip. He had no gastrointestinal complaints but gave a history of "stomach ulcers" 11 years previously. X-ray examination revealed a leather-bottle type of deformity of the entire stomach. The blood picture and other findings were not remarkable.

* References 4 and 8.

† References 4 and 5.

A total gastrectomy, splenectomy, and esophagoduodenostomy was done. There was no evidence of ulceration of the mucosa in the somewhat contracted, thick-wall, firm stomach. The enlarged nodes in the area were removed. The pathologist reported a highly anaplastic carcinoma of the stomach with the regional nodes involved.

Because of the usually hopeless prognosis in such cases of extensive and active carcinoma of the stomach, the patient was advised to dispose of his meat market and be prepared for an early

Case	T.F.C. 99603 M, 46
History	Epigastric pain, 2 yr.; tarry stools, 1 mo.
Physical findings	Epigastric tenderness
X-ray findings	Deformity and narrowing of distal 3rd of stomach
Operation	Partial gastrectomy; about 4/5th of stomach resected
Pathology	Small-cell lymphosarcoma
X-ray treatment	Yes
Course	L and W 2 yr.

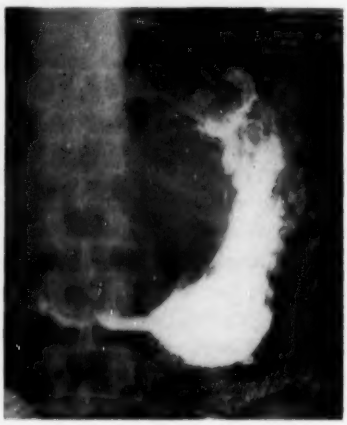

Figure 1

Case	W.L.H. 21240 M, 51
History	Lip crusting; no G.I. complaint; "stomach ulcers," 1938
Physical findings	Negative
X-ray findings	Leather-bottle type of deformity
Operation	Total gastrectomy and splenectomy
Pathology	Reticulum-cell lymphosarcoma
X-ray treatment	No
Course	L and W 4 yr.; 1½ yr. after surgery diagnosis changed to lymphosarcoma

Figure 2

death. Instead of deteriorating, he became stronger and gained some weight. One and one-half years later he was holding a job as milk distributor in a neighboring city.

The tumor committee, upon reviewing the sections in this case, reclassified it as reticulum-cell lymphosarcoma. Consultation by other pathologists confirmed this diagnosis. There often is confusion in the minds of pathologists in distinguishing highly cellular undifferentiated carcinoma from lymphosarcoma. It is important to

review the diagnosis whenever a patient with reputed carcinoma of the stomach lives well beyond the anticipated survival period. Especially is this essential when the lesion is anaplastic and chiefly mural.

Reflection upon this case discloses many items highly suggestive of lymphosarcoma: the absence of thought-provoking history, the unimpressive physical findings, the extensive roentgenologic findings well out of proportion to the symptoms, and the degree of mural infiltration without ulceration or involvement of the mucosa. The patient apparently is well somewhat beyond four years since his operation. The lower picture in Figure 2 is from a recent x-ray study of the esophagoduodenostomy, which functions well and shows no evidence of recurrence.

There seemed to be no good reason for giving x-ray treatment after one and one-half years when the true diagnosis was made. Irradiation will be given in the event of recurrence of the tumor. It is interesting to note that this case is one of

Case	C.W. 109916 F, 70
History	Weakness and weight loss, 1 yr.; abdominal cramps, 3 wk.
Physical findings	Mass, R.L.Q.
X-ray findings	Intussusception of ileum into cecum
Operation	Rt. hemicolectomy
Pathology	Small-cell lymphosarcoma
X-ray treatment	No
Course	L and W 11 mo.

Figure 3

reticulum-cell lymphosarcoma. Most reports in the literature ascribe a better prognosis to cases of the small-cell type.

Case 3.—This patient is the only woman in the group (Fig. 3). She also is the oldest, being 70 years of age.

A right hemicolectomy was done for a neoplastic lesion involving the appendix, tip of the cecum, and terminal ileum. The lymph nodes in the immediate vicinity of the primary tumor were involved, but those along the right colic vessels and base of the ileocecal mesentery did not show gross or microscopic evidence of metastases. Therefore, no x-ray therapy was administered in this case of small-cell lymphosarcoma. The patient apparently is well 11 months following surgery.

Case 4.—This 67-year-old man (Fig. 4) camplained initially of increasing gas formation in the bowel and constipation of six months' duration before seeking medical attention. The obstructive lesion of the descending colon, as shown in the uppermost x-ray study, was assumed to be carcinoma until the pathologist reported a small-cell lymphosarcoma with regional nodes involved.

Postoperative radiation therapy was given, and the patient did well for two years. Again increasing constipation prompted x-ray examination of the colon, with the resultant finding of a large filling defect in the transverse colon, as shown in the midright roentgenogram (Fig. 4). The lower left film study, showing essentially normal configuration, was made after x-ray therapy for what was assumed to be a recurrence of the lymphosarcoma.

The patient survived an additional 13 months before acute cardiac failure caused his death, with no apparent associated influence from the treated lymphoma. The patient died in another city, and, unfortunately, autopsy was not performed.

CASE 5.—A 54-year-old man (Fig. 5) had complained of abdominal pain for seven months and a small "lump" in the left groin for about two months. Sigmoidoscopic examination revealed countless numbers of what appeared to be benign, sessile, and pedunculated polypi of the rectum

Case	C.J.W. 63482 M, 67
History	Increasing gas formation and constipation, 6 mo.
Physical findings	Negative
X-ray findings	Obstructive lesion descending colon
Operation	Left colectomy
Pathology	Small-cell lymphosarcoma
X-ray treatment	Yes
Course	L. and W 2 yr.; recurrence in transverse colon; x-ray treatment; died in acute cardiac failure 13 mo. later.

Figure 4

Case	L.R.S. 101500 M, 54
History	Epigastric pain and bloating, 7 mo.; lump left groin, 2 mo.
Physical findings	Multiple polyposis by sigmoidoscopy, nodule left groin
X-ray findings	Polyposis entire colon
Operation	Biopsy, polyp of signoid and of groin gland
Pathology	Reticulum-cell lymphosarcoma
X-ray treatment	Yes
Course	Died of disease in 1½ yr.

Figure 5

and lower sigmoid. They ranged in size from a few millimeters to about 1.5 cm. Biopsy showed reticulum-cell lymphosarcoma, which also was the diagnosis of tissue from the enlarged nodule in the left groin. By x-ray (upper film, Fig. 5), multiple polyposis of the colon was found, with an almost complete obstructing lesion at the hepatic flexure.

X-ray therapy was begun with evidence of effective regression of the polypi of the colon (lower film, Fig. 5) and left groin nodule. He improved for about a year, but his condition

worsened thereafter. He died 18 months after the start of treatment. Autopsy revealed widespread metastases, indicating that this case terminated in a systemic disease. There is no available proof that the original neoplasm was in the gastrointestinal tract other than the initial findings of polyposis of the entire colon and the history of digestive symptoms early in his illness. This type of involvement of the colon is of exceedingly rare occurrence.

COMMENT

The diagnosis of lymphosarcoma of the gastrointestinal tract is most frequently made by the tissue pathologist and may be a complete surprise to the surgeon. Even the microscopic picture may be confusing at times, since experienced histopathologists may have difficulty occasionally in distinguishing lymphosarcoma from such lesions as endothelioma, noncaseous tuberculosis, rapidly growing carcinoma, and Hodgkin's disease.

X-ray studies may reveal filling defects along the alimentary tract with no specific indication of the nature of the pathology causing them. Most laboratory tests are disappointing as aids in diagnosis.

In a significant number of these cases, the tumors have been strangely localized and apparently not involved in a systemic disease. Therefore, the complete removal of an accessible mass and regional lymph nodes offers a reasonable chance for cure.

As I review my favorable experience in four or five cases of gastrointestinal lymphosarcoma in the light of that encountered by others, I am more optimistic about this sector of the malignant lymphoma problem.

DISCUSSION

DR. J. R. MCDANIEL, St. Joseph, Mo.: During the past year we have become greatly interested in unusual malignant lesions of the gastrointestinal tract because we have encountered four cases of primary malignant tumors of the small intestine—two sarcomas and two carcinomas.

Lesions of this type are quite rare, and the clinical problems of diagnosis and management merit brief comment.

[Slide] The first slide is from a 55-year-old woman who presented herself with the complaint of pain in the midepigastrum. She had had tarry stools and a marked anemia was present, but the x-ray studies were significant only in that they showed a small hiatus hernia. Because of the persistence of her anemia and tarry stools, a laparotomy was done, and an adenocarcinoma of the jejunum was found and removed.

[Slide] The next slide is from a 45-year-old man with a history of pain and tarry stools. The pain was in the right groin. Elsewhere, he had had a herniorrhaphy and an appendectomy, and at the latter operation a mass was found in the lower abdomen. He was referred to us, and we resected a tumor of the ileum, which proved to be a leiomyosarcoma.

[Slide] The next slide is from a 55-year-old man who gave a history of five months of weakness, pain, and tarry stools. X-ray examination of the gastrointestinal tract showed a deformity of the duodenum, without actual ulceration, and bleeding was attributed to duodenal ulcer. Subsequently, a mass developed in the epigastrum. He was operated on, and this leiomyosarcoma of the jejunum was removed.

[Slide] The last case is that of a 73-year-old woman who complained of anorexia, tarry stools, and weight loss. She had rather marked anemia. X-rays of the gastrointestinal tract were entirely negative. This patient was treated by transfusion. She returned seven months later with symptoms of small bowel obstruction and a palpable abdominal mass. At operation we removed an adenocarcinoma of the lower jejunum.

These patients with malignant tumors all had unexplained gastrointestinal hemorrhages. All had consulted physicians approximately six months before our operations. All had undergone

x-ray examination. This emphasizes the scarcity of early x-ray findings in tumors of the small intestine and the necessity for early surgical exploration when the source of gastrointestinal bleeding cannot be conclusively demonstrated.

DR. STANLEY R. MAXEINER, Minneapolis: I am very much interested in these reports. We have been extremely interested in the surgery of gastrointestinal diseases for many years.

With reference to the last speaker's essay, I would say that we had two patients with carcinoma of the cardia. One patient is living and well after seven or eight years, and the other one lived for seven or eight years and died last week. The survivor is working in a department store every day and has been in a gainful occupation for at least seven years.

In the last few years we have had five patients with sarcoma of the stomach. One patient had a leiomyosarcoma and lived less than a year. The second patient was operated on only a few months ago and is doing well. The third one had a lymphosarcoma of the stomach—so-called lymphoblastoma, Hodgkin's type—and we did a total gastrectomy; he survived only about a year. The fourth was a Negro boy who was working in Minneapolis; he had kissing ulcers on the lesser curvature. We did a total resection and a total gastrectomy; microscopic examination revealed lymphoblastoma. His home was in Houston, Texas. He returned there for x-ray management and we have not heard from him recently, but I think his outlook was very problematical.

The last and fifth case was that of a patient who had presented herself with a large upper abdominal tumor. We did an exploratory operation and found an involvement of the stomach, the transverse colon, and the upper jejunum. We removed practically all of the stomach, a major portion of the transverse colon, and about 15 to 20 in. (38 to 50 cm.) of jejunum. This patient survived the surgery, but survived her disease for only about a year.

DR. ORVILLE R. CLARK, Topeka, Kansas: I think that some of you may remember that at a meeting of this Association in St. Louis, which I believe was five years ago, Dr. Mills and I reported on a patient who had had two separate distinct lesions of the jejunum, each about a centimeter in diameter, polypoid in nature, the only symptom produced being that of extreme bleeding. These lesions had been removed on two separate occasions.

The pathology at that time was somewhat confused, but we had opinions that it was carcinoid lymphosarcoma, leiomyosarcoma, or metastatic melanoma. That was five years ago. You might be interested in knowing that this patient is still well and has never had any more bleeding, which has been something of a surprise.

DR. LAWRENCE CHAFFIN, Los Angeles: We have had a number of various types of sarcomas of the intestinal tract. I would like to tell you of just one case in which exploration was done for diagnostic purposes and the patient was found completely inoperable, with a complete involvement of the stomach from one end to the other, with nodes along both lesser and greater curvatures.

This patient is now living and well and is working as a police officer, after x-ray treatment alone, after diagnostic biopsy. These tumors behave in a very peculiar manner.

DR. J. C. THOMAS ROGERS, Urbana, Ill.: I wish to thank the discussants for their contributions on this subject.

The terminology for malignant lymphomata is quite confusing, due largely to variations in the several proposed classifications. According to Anderson, the lymphosarcoma and lymphoblastoma are malignant deviations from the lymphocytic phase. On the other hand, the reticulum-cell type of malignant lymphoma arises from the fine stromal elements of lymphatic germinal centers.

From the surgeon's point of view, the matter of classification is not of prime importance in cases of malignant lymphomata of the gastrointestinal tract. The more practical issues are the extent of extirpation of the tumor and regional lymph nodes and the postoperative use of x-ray therapy. As has been mentioned, we have chosen to give x-ray therapy only in those cases in which known involved nodes were left behind.

It should be pointed out that a tumor in the gastrointestinal tract of a child is generally considered lymphosarcoma until proved otherwise. According to most observers, the contrary assumption obtains in adults. In all cases the problem of systemic involvement must be solved before surgical treatment is contemplated.

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MANAGEMENT OF GANGRENOUS INTUSSUSCEPTION IN INFANTS

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DISCUSSION continues at the present time as to the best means of dealing with the young child who has an irreducible or gangrenous segment of ileum or cecum resulting from intussusception. Three methods are employed and are still debated: (1) primary resection and anastomosis; (2) two-stage resection and anastomosis (Mikulicz), and (3) lateral anastomosis leaving the intussusception in situ.

Primary resection and anastomosis is obviously the ideal method of treatment if it can be performed safely, but before accepting it as the routine treatment it is advisable to consider the problem in two ways:

1. The local hazard: the technical difficulties and risks involved in anastomosing the bowel immediately after excision of the infarcted or gangrenous segment.
2. The general hazard: the state of illness of the child.

The first danger is not insuperable. The literature contains several accounts of single cases in which primary resection and anastomosis has succeeded in children, and Dennis' (1947) achievement in performing without fatality such resection in seven infants, five of whom had irreducible or gangrenous intussusception, is well known.

With such technique as Dennis describes, the local problem of resection and immediate anastomosis can be successfully solved, but there remains the problem of the child's general condition. The degree of illness of the young infant with a gangrenous or irreducible intussusception is variable, but it can be extreme, and the illness cannot be expressed only in terms of electrolyte balance or corrected by gastric suction and intravenous salt solutions. It is a confession of our ignorance of the underlying disturbance to have to say that such an infant has reached the stage of exhaustion and may be able to stand very little further exertion, whether caused by illness or by surgery. It is unusual for resection and anastomosis to be completed in under an hour, and an hour's surgery and anesthesia may be the final injury that turns the scales against the patient. In the surgical department in Newcastle-upon-Tyne Hospitals, during 1949 to 1950, three infants were operated upon for this condition who died in similar fashion shortly after surgery. They were desperately ill babies on admission. They were resuscitated as well as possible; the stomach was kept empty by an indwelling tube, and dehydration and electrolyte balance were corrected by intravenous fluids over a 6 to 8 hour period. Primary resection and anastomosis of an irreducible segment of bowel was performed by experienced abdominal surgeons. Each child died in a similar way, never fully regaining consciousness and developing a pyrexia (temperature 105 to 107 F.)

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Read at the Sixty-First Annual Meeting of the Western Surgical Association, Chicago, Dec. 5, 1953.

before death, about 12 hours after operation. Autopsy added no new information. They died because they were too ill to stand the surgical treatment that was carried out.

Could such infants be made safe for definitive surgery by better and more prolonged preoperative treatment? It did not seem to us that they could be, and if they could not, could surgery be reduced to the essential minimum of relieving the obstruction and removing the gangrenous segment, and by so doing obtain a patient who lived to fight another day? This is simply a return to the old two-stage Mikulicz resection, which had the sanction of a previous generation in surgery and has recently been practiced with success in the condition of intussusception at the Boston Children's Hospital (Gross and Ware, 1948; Gross, 1953).

The danger of an ileal fistula, resulting from a two-stage resection in an infant, has been stressed—possibly overstressed, especially when the fistula is to be open for only a short period of days. Wangensteen, writing in 1937, finds that he is not impressed by the dangers of such a fistula. Similarly, Gross and Ware, in 1948, report no difficulty in making good the loss of fluid and electrolytes from an ileostomy

TABLE 1.—*Age and Duration of Symptoms Before Admission*

Patient	Age, Mo.	Time from Onset of Symptoms to Hospital Admission, Hr.
1	3	28
2	4	48
3	4	42
4	5	77
5	7	10
6	11	86
7	19	36
8	21	64
9	33	48
10	48	42

in an infant. Increasing experience in the management of fluid and salt balance in babies makes it possible to approach the problem of a short-term ileostomy with some confidence and free from the old sense of hazard.

It was therefore decided to carry out the two-stage operation in an infant whenever resection of the terminal ileum or ascending colon was needed for irreducible or gangrenous intussusception; careful thought was given to making the steps of surgery as simple and brief as possible. Ten babies or young children were operated upon. Their ages and the time from onset of symptoms to admission to hospital are shown in Table 1. Eight of the 10 patients were extremely ill, and three of these were desperately sick. All were prepared for surgery by gastric aspiration and intravenous fluid, and all required resection of the terminal ileum or of the ileum and ascending colon for intussusception that was irreducible or gangrenous. In each case a two-stage resection was performed by one of the past or present members of the surgical staff of the department of surgery, Royal Victoria Infirmary, in Newcastle-upon-Tyne, during the years 1951 to 1953. There was no death in the series.*

* During the period 1951-1953 an 11th child was operated on for gangrenous intussusception (by a two-stage procedure), for which a total colectomy was performed. The child died of difficulties in anastomosing the ileum to the rectal stump. The case is not included in this series, which is concerned with the common problem of the irreducible or gangrenous segment of bowel in the ileocecal region.

At operation, with the patient under open ether anesthesia, a short, right paramedian incision was made, two fingers introduced into the abdomen, and the intussusception milked back toward the cecum. When complete reduction proved impossible, the irreducible segment was gently lifted into the wound, examined, and further reduction performed if feasible. If obvious gangrene was present (five cases) or if the condition proved irreducible after several minutes (five cases), a decision was promptly made for resection. A restraining moist pack was placed in the wound over any exposed bowel, and the mesentery of the involved segment was divided and the vessels secured; light clamps were applied at the limits of excision, and the affected segment was cut off, the assistant holding the clamps clear of the wound so that about ¾ in. (2 cm.) of healthy bowel protruded. By suitable no-touch technique and handling of instruments, it was a simple matter to excise the bowel without touching or soiling of any part of the wound or of the surgeon. No attempt was made to suture together the two limbs of the ileostomy (or ileocolostomy), for this takes time and may predispose to ileus by handling. For the same reasons, no fixation stitches were passed between the bowel and the body wall. The assistant held the two emerging portions of intestine by their clamps so that the limbs were touching along their mesenteric surfaces and emerged at one end of the wound, protruding for the distance described. The body wall was then closed in layers around them, making the closure snug, yet without constricting the bowel. A skin dressing was applied with gauze and "Elastoplast," and drainage tubes of glass (Paul tubes) or rubber catheter were then tied into the exposed bowel ends and led off to suitable containers.

The whole procedure was simple, gentle and speedy, and contained the bare minimum of manipulation and exposure and of anesthesia. There was no haste to move the child from the operating table, for even lifting does harm during the first critical hours. The patient was therefore covered with a thin towel, free air circulation encouraged because of the danger of hyperthermia, and gastric suction and intravenous fluid maintained. The child was returned to the ward when it seemed safe to do so. Such minimal surgery and disturbance in our series did not make the general condition appreciably worse than it was before operation.

A little improvement was noted in about 12 hours, and discharge of ileal contents began to be free during the next 12 hours. By the 24 to 48-hour period after surgery, anxiety was lessening, and, as the distention collapsed, the child's condition improved rapidly. Fluids were given by mouth as soon as ileal discharge was established, and intravenous-fluid therapy continued in accordance with clinical judgment, with some reliance also on the results of laboratory determination of blood sodium, potassium and alkali reserve, and the hematocrit value.

It seemed wise to us to close the ileostomy as soon as it was judged that the child was fit to stand this further procedure. In 8 of our 10 babies this was done at about the 48th hour; in one instance, in 72 hours. At this time the small bowel was emptying freely through the drainage tubes, which were still secure within it, and there was no discharge of ileal contents onto the skin. At operation the emerging bowel was trimmed off between clamps, the wound reopened, the bowel ends freed with the finger and then closed, and continuity reestablished by lateral anastomosis. Any available omentum was wrapped around the suture site and the body wall

closed in layers without drainage. This operation did not cause anxiety either on the operating table or subsequently. An ileus usually developed for one to two days, which responded to "nonintervention" by avoiding mouth feeding and giving intravenous fluids. Penicillin was given parenterally. Two patients developed mild wound infection. One patient had a fecal leak which closed spontaneously. These nine patients left the hospital fully healed and on the normal diet for their ages in the following times, as shown in Table 2.

In the 10th child (the only instance of its kind), the surgeon had attempted to fashion a self-closing ileostomy. After the spur was crushed, the ileostomy discharged less freely, and the child left the hospital in 16 days but had to be readmitted for surgical closure of the fistula at the seventh week.

COMMENT

From the experiences reported by other workers of the result of primary excision and anastomosis in treatment of an irreducible or gangrenous intussusception in an infant, it can be accepted that a primary repair may be carried out safely and

TABLE 2.—*Duration of Hospital Admission*

Patient	Age, Mo.	Days in Hospital
1	3	13
2	4	16
3	4	29 *
4	5	14
5	7	16
6	11	15
7	21	14
8	33	12
9	48	14

* Fecal leak.

is the method of choice if the child is in satisfactory condition to stand the operative incident. If the child's condition is poor, however, it may be wise to do the least possible at the first operation, and the essence of the attitude described in this paper is that in such circumstances the operation shall indeed consist of the minimum possible—in full agreement with the observations of Gross and his colleagues that the time factor on the operating table is particularly important and that it is the policy to do no more than is absolutely necessary. Lateral anastomosis (with or without exteriorization of the irreducible segment) as practiced by White and Dennison (1952), although from their report clearly a lifesaving procedure in many instances, does not fulfill these criteria. The "aseptic" two-stage resection advocated by Gross (1953) in his classic text of children's surgery, with approximation by suture of the two emerging limbs of bowel, adds a step to the operation and was not done in this present series, in order to save time and manipulation and so lessen the immediate hazard, as well as to reduce the danger of ileus at a time when prompt discharge of the obstructed contents of the ileum was all important; and also because with suitable technique it seemed possible to do the quick "open" two-stage resection without the risk of serious wound and peritoneal infection that had been previously reported.

It is reasonable to conclude that as between excision with immediate anastomosis and the two-stage operation outlined here it is largely a matter of surgical judgment, a matter of knowing when to be bold and when cautious. The experiences described in this paper demonstrate that even in an extremely ill child the cautious approach can be successful, and has its place in the management of this difficult problem.

SUMMARY

Ten cases are reported of infants and young children on whom a two-stage resection of ileum or of ileum and ascending colon was carried out for irreducible or gangrenous intussusception.

The first operation consisted of the bare minimum—excision of the segment, exteriorization of the bowel ends without suturing together of the loops, and drainage into containers.

The ileostomy presented no difficulty in management. It was closed in about 48 hours, when the child's condition had become satisfactory.

There was no death in the series.

While primary resection and anastomosis is the ideal method of treatment when the child is a good risk, a two-stage operation as described is advocated if the infant's general condition is poor.

DISCUSSION

DR. JOHN M. WAUGH, Rochester, Minn.: I am sure you all feel as I do, that it is a real privilege to hear from one such as Dr. Bentley, who has had such a tremendous experience with this ailment.

I am glad that he has emphasized that the important thing to remember in emergency surgery is to save a life and not necessarily to correct a diseased organ. The cure can be effected often with a later procedure with less risk.

That certainly holds true for a badly infected, gangrenous gall bladder in a poor-risk patient. It holds true in many other situations.

I am sure there would be many less common duct strictures sent to the various centers for repair if it were remembered that one is saving a life and not correcting a diseased situation and that cholecystostomy is still occasionally advisable in acute cholecystitis. I think that those of us who were brought up in the Mikulicz era sometimes forget it is a lifesaving procedure. I was astonished the other day when we used this procedure after an extensive operation, and I did not think that the patient could stand a primary anastomosis in the sigmoid after the extensive removal of the pelvic organs that we had done, and my assistant said it was the first one he had seen. I think we ought to emphasize to these younger men who are doing, by and large, most of the emergency work that the Mikulicz procedure is a very valuable operation, and they should not feel that they have to do a definitive operation, or that they are going to be criticized if they do not do an immediate anastomosis; they should feel free to use the exteriorization method when it is indicated.

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PNEUMATOSIS CYSTOIDES INTESTINALIS

Report of a Case

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FORT SMITH, ARK.

PNEUMATOSIS cystoides intestinalis, also known as gas cysts of the intestine, is considered to be a rare pathological condition. Bang,[1] in 1876, first published a report of its occurrence in a human being, and it has been recognized to occur in swine for a number of years, usually associated with a catarrhal enteritis. There have been fewer than 50 cases recorded in the American literature, the most recent being reported by Appleby [2] and also by Sherwin and Messe.[3] Finney,[4] in 1908, reported the first American case. Jackson,[5] in 1940, presented the 4th case in this country, bringing the total number of recorded cases to 172 at that time. The condition is rarely diagnosed before operation. Reverdin,[6] in 1924, diagnosed the first case confirmed by surgery. In 1949 the first American case was diagnosed by x-ray study, preoperatively, by Gazin, Brooke, Lerner, and Price.[7]

Several reports have originated from the Far East,* but the disease is a very rare one and few authors have had experience with more than one or two cases. The condition is known to occur most frequently in conjunction with chronic obstruction of the upper gastrointestinal tract, produced by peptic ulcer or carcinoma. It has also been known to occur in association with diarrhea. Botsford and Krakower [10] reported on six cases occurring in infancy, most of which were associated with a severe enteritis or vomiting.

PATHOLOGY

Characteristically, the condition is a collection of multiple thin-walled, gas-filled cysts, varying in size from a few millimeters up to several centimeters in diameter. In most instances these cysts form a grape-like cluster, resembling a hydatid mole, but they can occur singly. They are usually located in a specific segment of the bowel, occurring most commonly in the small intestine and quite frequently in the terminal ileum. Occasional cases have been reported in which these cysts occur in the large bowel or in other portions of the small intestine. In adults the cysts are usually located subserosally, but they may extend into the areolar tissues of the mesentery and extraperitoneal areas. In infants the cysts are apparently predominantly submucosal. Microscopically, the cysts appear as thin-walled sacs consisting of connective or endothelial-like tissue with giant cells present. Some observers have noted round-cell infiltration and fibrosis of the cyst wall. Serous fluid may also be found to be contained in the interior of the cysts. The chemical composition of the gas enclosed in these cysts does not appear to be that of the intestine. Analyses have

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* References 8 and 9.

shown that it contains 70 to 90% nitrogen, 0 to 15% carbon dioxide, and 3 to 20% oxygen.[11] There have been no constant bacterial findings of the contents of these cysts, and apparently no infection has been prevalent in any of the reported cases.

ETIOLOGY

Numerous theories have been put forward to explain the etiology of these cysts, but none of the theories have been consistent or proved.

The bacterial theory lacks confirmation because spreading infection has not been found, and there have been no consistent organisms cultured from the interior of the cysts.

The neoplastic theory presumes the existence of a specific type of cell capable of secreting gas, but there has been lack of any satisfactory evidence to substantiate this assumption.

Many authors have held to a mechanical causation of this disease. Perhaps the most logical assumption is that air is forced through the stomach wall through minute abrasions caused by overdistention produced by the obstruction, and here it is carried, either by the lymphatics or perilymphatics, to distant areas in the intestinal tract.† Experimental work has, however, failed to bear out this theory, and the exact etiology remains considerably in doubt.

Some veterinarians have proposed a dietary causation of this condition, and their suppositions are enhanced by the fact that a large percentage of swine fed on polished rice will develop the disease.[14] In human cases, Freedlander and Teitelbaum [15] suggest a nutritional factor, probably on the basis of an avitaminosis.

DIAGNOSIS

There are no apparent typical clinical findings in pneumatosis cystoides intestinalis. It is usually an incidental finding at surgery or autopsy. As stated above, it occurs most generally in conjunction with some chronic obstructing lesion of the upper gastrointestinal tract or in association with enteric diseases of childhood. Of 44 American cases, only 8 were found at surgery and only 4 of the total number had been diagnosed preoperatively by x-ray study.[3]

Roentgenologists are becoming increasingly aware of its presence. The gas cysts themselves can be seen by x-ray examination. The gas itself apparently may dissect its way retroperitoneally and may accumulate between the parietal peritoneum and muscular layer of the diaphragm, giving an appearance of a pneumoperitoneum.[7] It would seem likely that an actual pneumoperitoneum could be produced by rupture of the air cysts themselves, as they are very thin-walled.

Perhaps the only clinical symptom which this disease alone could produce would be that of mechanical bowel obstruction due to encroachment of the lumen of the intestine by great numbers of these cysts.

TREATMENT

Cases in which gas cysts are generalized or very widespread are not suitable for resection, since an unusually large portion of bowel would have to be removed in order to eliminate the disease entirely. Where the cysts are localized to a fairly small segment of bowel, resection is usually feasible, especially where it seems as

† References 12 and 13.

though obstruction could be produced by extraluminal pressure by the mass of cysts. It has been found by several authors that upon reexploring an abdomen where gas cysts had been present and a concomitant obstruction of the upper gastrointestinal tract was relieved, that on subsequent reexploration the cysts were found to be resolved.‡

REPORT OF CASE

B. D., #93165 (referred by Dr. Earle Hunt, Clarksville, Ark.), an 8-year-old white girl, was admitted to Sparks Memorial Hospital on Aug. 11, 1952. The history, as obtained from her mother, was that the child had been a feeding problem since birth and had vomited at frequent intervals as an infant. Since the age of 9 months she had suffered intermittent episodes of vomiting, which the mother stated had been very severe, and she would recognize food in the vomitus that had been eaten as long as a week previously. The mother stated that before

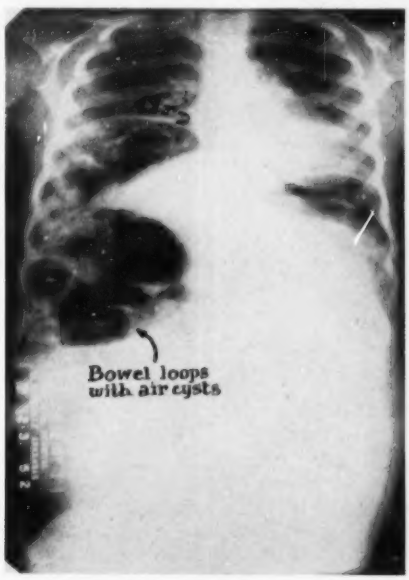

Fig. 1.—Flat plate of abdomen, showing marked elevation of both diaphragms and what appears to be free air under the domes of both diaphragms, suggesting a pneumoperitoneum. Interposition of many gas-filled loops of bowel between the right diaphragm and the liver is noted. These are surrounded by multiple air spaces which, in retrospect, could be interpreted as multiple air cysts. Displacement of the liver out of its normal position toward the left side is also noted.

vomiting the child's abdomen would become greatly distended, and the vomitus was regarded by her as being tremendous in quantity. She noted "lumps" in the child's abdomen at frequent intervals, which moved from place to place. The child had been constipated all her life and had to be given laxatives for relief. To the mother's knowledge the child had never had any pain up until about 10 days before being admitted to the hospital, when she appeared to have some distress and woke up, according to her mother, "beating her stomach." A bubbling sound in the child's abdomen had been noted on occasion. The child would go for two or three weeks without vomiting and then would belch malodorous gas and vomit a tremendous amount.

Physical examination revealed a fairly thin, white girl, who appeared to be intelligent and cooperative. The abdomen was diffusely distended, particularly in the upper region in both

‡ References 5 to 16.

quadrants. There were no masses or areas of tenderness palpable. The peristaltic sounds were normal. The rib margins on both sides appeared to be flared to an unusual degree, as a result, probably, of chronic distention. After nasogastric suction the abdomen was again examined a few hours later, and the distention had completely disappeared.

Routine laboratory work revealed the urinalysis to be essentially normal. The red cell count was 3,700,000, with 68% hemoglobin; the white cell count was within normal limits. A flat plate taken of the abdomen on admission (Fig. 1) revealed tremendous distention of the stomach and duodenum. There were interposed loops of small bowel between the dome of the right diaphragm and the liver. There also appeared to be free air present beneath the diaphragm. A gastrointestinal series (Fig. 2) revealed the presence of a tremendously enlarged duodenum, with apparent partial obstruction at the third or fourth portion. The duodenum appeared to be as large or larger than the stomach, and it looked as though actually there were two stomachs visualized.

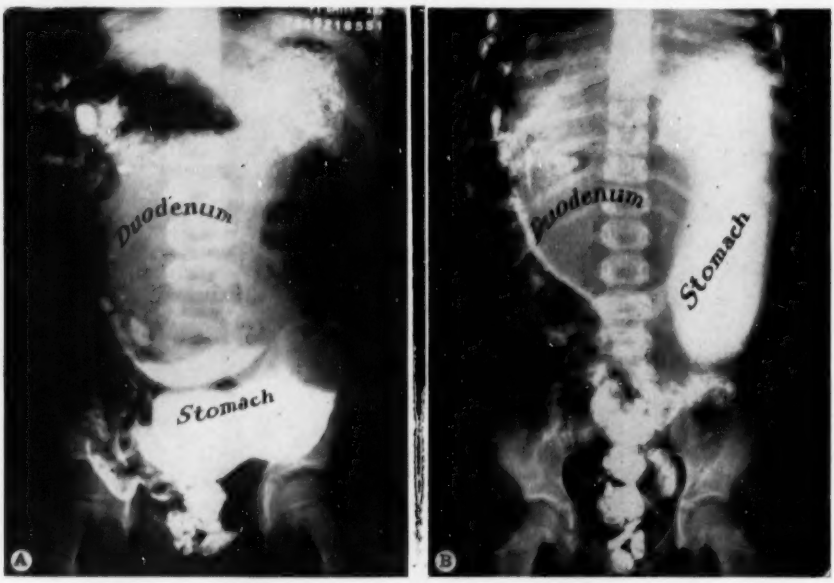

Fig. 2.—*A*, gastrointestinal series, showing a greatly enlarged and ptotic stomach occupying the left side of the abdomen, with a portion of the stomach located in the pelvis. Central portion of the abdomen is occupied by a tremendously enlarged duodenum containing three distinct layers: below, a small barium layer; in the midportion, a fluid layer, and in the uppermost portion, a gas layer.

Fig. 2.—*B*, roentgenogram taken six hours following barium administration, with the patient in the supine position. This film reveals a large amount of retained barium within the stomach, and the tremendously dilated duodenum is again noted, which contains a large amount of air. Multiple distended bowel loops are seen in the right abdomen along the right lateral wall.

Laparotomy was performed on Aug. 13, 1952. At the time of surgery it was found that the first, second, and third portions of the duodenum were tremendously dilated and somewhat thick-walled (Fig. 3). There was a partial obstruction found at the third portion of the duodenum, apparently caused by a congenital kinking. The duodenum was actually as large or larger than the stomach itself. In the terminal ileum, beginning about 12 in. (30 cm.) from the ileocecal valve and extending for a distance of 6 to 8 in. (15 to 20 cm.), there were multiple cystic grape-like clusters which appeared to arise from beneath the serosa of the bowel and extended into the mesentery (Fig. 4). These appeared to be filled with air and gave an unusual "bubbly" appearance. There was some abnormality in the rotation of the large bowel, as the

cecum was situated in the right upper quadrant. The liver appeared to be displaced somewhat medially and downward, with loops of small bowel being present under the right diaphragm. A side-to-side duodenojejunostomy was performed, two inner layers of atraumatic chromic

Fig. 3.—Showing the tremendously enlarged duodenum with the pointer indicating the location of the partial obstruction which has been relieved.

Fig. 4.—Showing the appearance of the gas cysts of the terminal ileum at the time of surgery.

absorbable surgical (gut) and one outer layer of interrupted nonabsorbable surgical (silk) suture material being used. The anastomosis was made unusually wide. A resection of the involved portion of terminal ileum was done to include all the gas-filled cysts, and gastrointestinal continuity was reestablished by means of an end-to-end anastomosis, with use of one inner layer of atraumatic chromic gut and one outer layer of interrupted silk. An appendectomy was

then performed in the usual manner. The patient left the operating room in good condition. After surgery the child made an uneventful postoperative recovery, and she left the hospital 14 days following operation. The child has been asymptomatic since surgery. She has had no further attacks of vomiting or of abdominal distention and appears to be in excellent health.

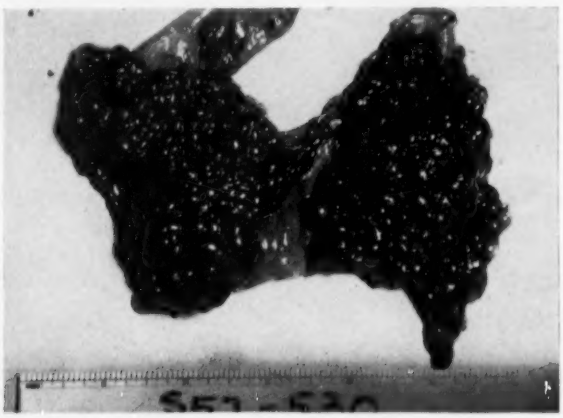

Fig. 5.—Resected specimen of terminal ileum with gas cysts.

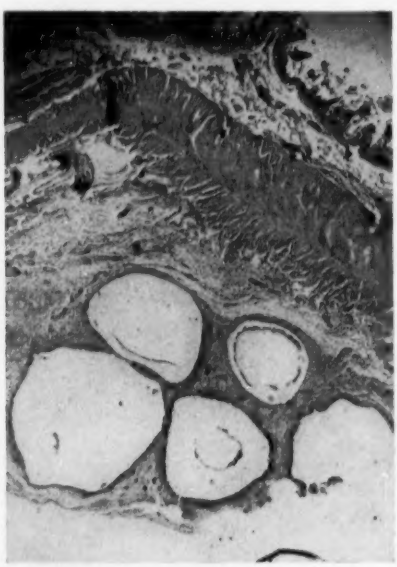

Fig. 6.—Microscopic appearance of resected specimen.

When the specimen was examined, it was found that the lumen of the bowel was patent, but in the areas where the greatest number of air sacs were found, the mucosal pattern of the ileum was distorted by blebs of air beneath the mucosa. There was no evidence of any erosion of the mucosa. There was definite encroachment of the lumen produced by some of the larger cysts (Fig. 5). The microscopic appearance (Fig. 6) was that of air-filled cysts, varying in size from 1 mm. to several centimeters in diameter. The cysts were lined with well-defined

endothelial cells, and numerous foreign-body giant cells were present. The connective tissues were somewhat edematous and infiltrated with round and lobulated inflammatory cells, the latter consisting principally of eosinophiles, but there was no pronounced active inflammatory process.

SUMMARY AND CONCLUSIONS

A case of pneumatosis cystoides intestinalis has been presented, which occurred in an 8-year-old girl. The concomitant obstruction was discovered to be located in the third portion of the duodenum and was undoubtedly congenital.

Pneumatosis cystoides intestinalis is a rare condition, there being fewer than 50 cases reported in the American literature. Most of these cases have been reported at autopsy.

Most cases of pneumatosis cystoides intestinalis appear either in conjunction with an obstruction of the upper gastrointestinal tract, such as that produced by an obstructing duodenal ulcer or by carcinoma of the pylorus. It may also occur with an enteritis.

The exact etiology of this condition is not understood. The mechanical and dietary theories probably afford the most widespread acceptance.

Even though only a few cases have been diagnosed preoperatively, it is possible to do this radiologically, and roentgenologists are becoming more aware of its presence. The exact clinical significance is, perhaps, not too well understood, and the main reason for resecting a portion of the involved bowel would be for the prevention of a possible obstruction. Cases have been reported in which the accompanying obstructing factor has been removed, and on subsequent laparotomy the cysts were found to have resolved.

DISCUSSION

DR. FRANCIS H. STRAUS, Chicago: It is with some hesitancy that I report some animal experiments I made many years ago on this problem, which were instigated in my mind during exploration of a closed-loop obstruction with the intention of making a cecostomy for a closed-loop carcinomatous obstruction of the large intestine.

When I opened the peritoneum, my face was blasted with gas, which I thought was from the cecum I might have opened, until I noticed that the gas had no odor. In continued the investigation and found the patient had a spontaneous pneumoperitoneum and, beneath that, a greatly distended large intestine. A cecostomy was done.

I became sufficiently interested in this problem that I got some dogs and attempted to reproduce the situation by making closed-loop obstructions of the large intestine. As you know, the large intestine of the dog is not at all comparable to that of the human, and these experiments were not successful. However, if the large intestine of the dog is made into an artificially closed loop by obstruction proximally and distally and air under pressure is introduced into the lumen of the bowel, after a time air can be seen gradually going through the lymphatics of the mesentery of the bowel and making gas-filled cysts. If the pressure is continued these gas-filled cysts rupture to the outside, and the air escapes from the lumen of the bowel into the peritoneal cavity.

It is not hard to visualize what occurs in these circumstances. The tension within the bowel —and ulcers, if ulcers are present—ruptures minute areas of the mucosa, and the air obtains access to open lymphatics, distends them in some areas, and finally ruptures them.

I did not report this work because I think the series of experiments I did was inconclusive, but I think it is a lead or an indication of the possible mechanism in some of these cases.

DR. GUY V. PONTIUS, Chicago: About three years ago a patient was sent to me with a diagnosis of carcinoma of the descending colon. His only symptom had been that of bleeding.

On exploring his abdomen, we encountered such a picture as Dr. Olson showed. For a distance of about 4 in. (10 cm.) the colon was markedly studded with air cysts. The interesting

thing is that this man was in perfectly good health. He had a complete gastrointestinal study, and there was no evidence of obstruction other than this one lesion; consequently, I thought it was feasible to resect it, which I did, and I did an end-to-end anastomosis. He has remained in good health since.

He had a normal convalescence, but, interestingly enough, his colon now—from the point of the anastomosis, which was about midsigmoid, to the hepatic arch—is markedly involved with more air cysts. We can see that the site of the anastomosis is not obstructed. He eats well. He occasionally has a little diarrhea. He has no more bleeding, is 68 years old, working, and very happy.

DR. JOHN D. OLSON, Fort Smith, Ark.: One interesting point to me about this disease is that there is no infection present. If there is a connection between the gastrointestinal tract and the cysts, it would appear to me that infection should occur.

A second interesting point is the fact that foreign-body giant cells are present, which proves that air acts as a foreign body.

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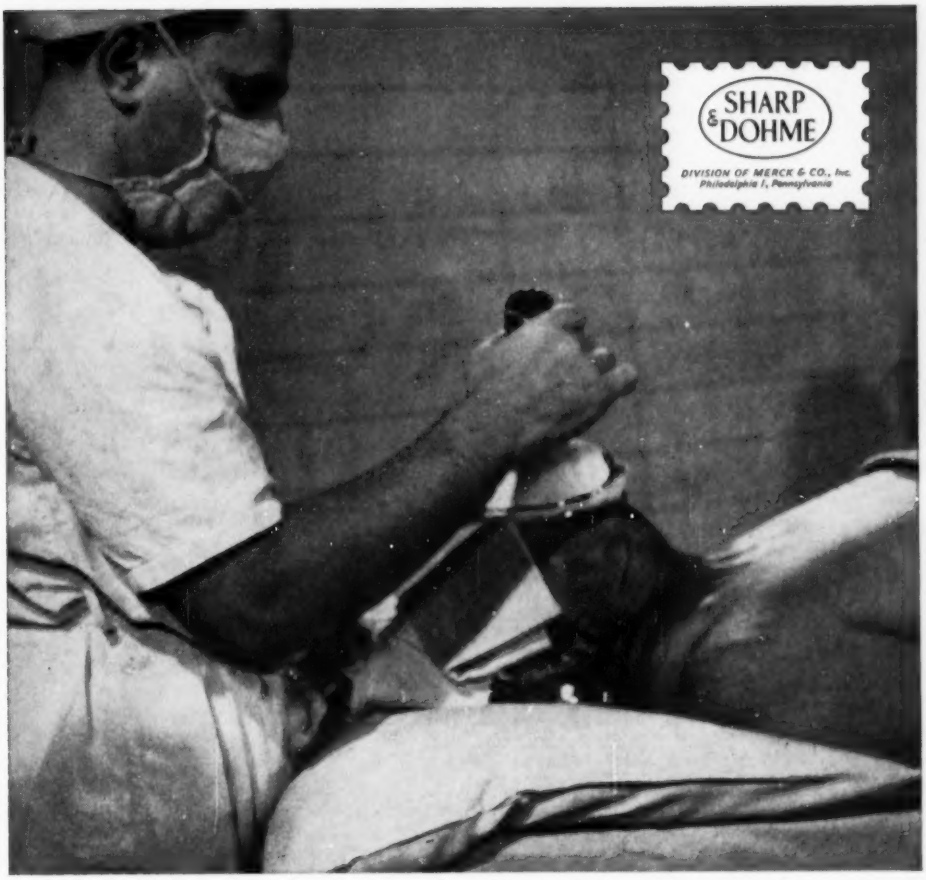

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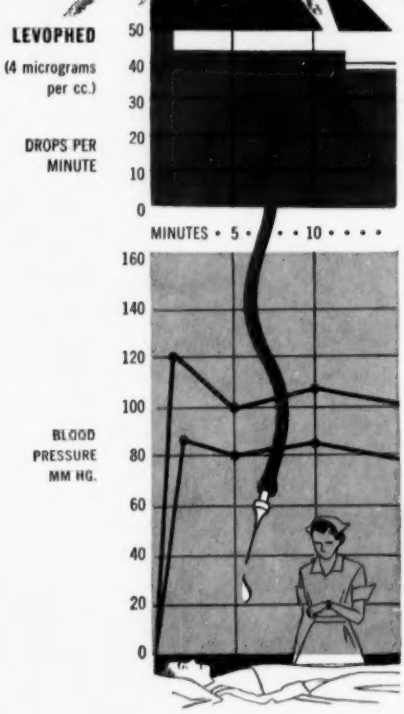

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